IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of: Judith ARONHEIM et al. Application No.: 10/045,510 Filed: October 19, 2001	Art Unit : 1621 Examiner : Samuel A. BARTS

For: CRYSTALLINE VENLAFAXINE BASE AND NOVEL POLYMORPHS OF VENLAFAXINE HYDROCHLORIDE, PROCESSES FOR PREPARING THEREOF

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APPEAL BRIEF

Appellants respectfully submit this Appeal Brief pursuant to 37 C.F.R. § 41.31 in support of the allowability of their pending claims, which have been at least twice rejected on the same grounds. The Appellants filed a Notice of Appeal on June 27, 2005. The fee under 37 C.F.R. § 41.37 is provided concurrently herewith.

REAL PARTY IN INTEREST

The real party in interest for U.S. Patent Application Serial No. 10/045,510 is:

Teva Pharmaceutical Industries, Ltd.
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P.O. Box 3190
Petah Tiqva 49131
Israel

RELATED APPEALS AND INTERFERENCES

There are no other prior or pending appeals, interferences or judicial proceedings known by the undersigned, or believed by the undersigned to be known to Appellants or the assignee, "which may relate to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal."

STATUS OF CLAIMS

Claims 1, 2 and 95-98 are pending. Claims 3-94 have been withdrawn from consideration. Claims 1-2 and 95-98 are under rejection and on appeal. Text of the pending claims is provided in the Claims Appendix.

STATUS OF AMENDMENTS

An Amendment under 37 C.F.R. §1.116 was filed June 27, 2005 requesting reconsideration of the pending claims but was not entered.

SUMMARY OF THE INVENTION

The claimed subject matter of the present invention relates to white crystalline venlafaxine and venlafaxine prepared by a method of the invention. Venlafaxine has the chemical formula (±)-1-[2-(Dimethylamino)-1-(4-ethyoxyphenyl) ethyl] cyclo-hexanol. For the purposes of this appeal, the claims have been divided into two groups:

1) Independent claim 1 and dependent claim 2 directed to venlafaxine in white crystalline form; and

2) Independent claim 95 and dependent claims 96-98 directed to venlafaxine prepared by processes recited therein.

Venlafaxine in white crystalline form (Group 1) is disclosed in the specification, for example, on page 2, lines 7-9 as well in on page 6, lines 9-11 and also in Example 1, page 7, line

9. A powder x-ray diffraction pattern of crystalline venlafaxine base is provided in Figure 9 as described in page 5, line 24 of the specification.

Venlafaxine prepared by a method of the invention (Group 2) is disclosed, for example, on page 6, lines 12-18 of the specification. The claimed method is also described in Example 1, page 6, line 28 to page 7, line 10.

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Whether claims 1 and 2, which stand rejected under 35 U.S.C. § 103, are *prima facie* obvious in view of WO 00/32555.

Whether claims 95-98, which are product-by-process claims rejected under 35 U.S.C. § 103 are *prima facie* obvious in view of WO 00/32555.

GROUPING OF CLAIMS

Groups 1 and 2, claims 1, 2 and 95-98, stand or fall together.

ARGUMENT

Rejection under 35 U.S.C. § 103 over WO 00/32555

Claims 1, 2 and 95-98 stand rejected under 35 U.S.C. § 103 as *prima facie* obvious over WO 00/32555 ("the '555 publication," attached hereto as Exhibit 1). *See* August 1, 2005 Advisory Action. These claims are directed to venlafaxine base "in the form of white crystals." The '555 publication discloses venlafaxine base as a "yellow gum that turned slowly in to [*sic*] a pale yellow solid." The '555 Publication, p. 23, line 24.

A. A Colorless (White) Form of a Known Compound is not Prima Facie Obvious Over a Colored (Yellow) Form of the Compound

1. Background

Patentability of Applicants' claims does not turn on the purity of their venlafaxine base ("venlafaxine") alone. The Office acknowledges that Applicant's invention is not directed to the mere purity of venlafaxine, but to a difference in both color and crystallinity. *See* December 28, 2004 Office Action, p. 2.

But in rejecting Applicants' claims to white crystalline venlafaxine over the yellow solid of undisclosed crystallinity in the '555 publication, the Office mistakenly equates color with general purity, discussed *infra*, alleging that "Applicant has done nothing to make the crystals white other than purifying venlafaxine base." *Id.* The Office further states that "color is simply an inherent property" of purity, and that "mere purity of compound, in itself, does not render a substance unobvious." *Id.*

It is clear that the Office has rejected the claims on appeal as *prima facie* obvious on the ground that white crystalline venlafaxine is merely a more pure form of a known compound. Applicants hereby argue accordingly.

2. Proper Application of the Prescript of M.P.E.P. § 2144.04 VII[1] that Mere Purity Does Not Render Patentable a Purer Form of a Known Compound Requires that "Purity" be Construed as "General Purity" or "Assay"

"Purity" does not have an immutable definition. The different connotations for the term "purity" in the chemical and allied arts is succinctly summarized by BASF Aktiengesellschaft, The Chemical Company, in its Frequently Asked Questions (FAQ):

> What exactly is purity? Most people would define purity by the actual content of the desired compound expressed in weight percent . . . **Weight % is only one of many possible definitions of purity**. A catalysis chemist would define purity as being **free of** any coordination species, like halides which deactivate the metal by formation of stable complex compounds. An electrochemist would define purity by **having no oxidisable impurities** which narrow down the electrochemical window. An engineer might prefer not to have impurities that affect the viscosity and finally the end user will define purity as being **free of** residual potentially toxic alkylating agents. These examples show, that only the targeted application defines what purity in this case means.

BASF Aktiengesellschaft FAQ, http://www2.basf.de/en/intermed/nbd/products/ionicliquids/faq.htm?id=V00-cK1th82Yqbw22XQ#2c, p. 3 (emphases added) (attached hereto as Exhibit 2).

The conflict between the different uses of the term "purity" is also acknowledged by the chemical company Fisher Scientific International, which in its product literature Frequently

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[1] "Pure materials are novel *vis-à-vis* less pure or impure materials because there is a difference between pure and impure materials. Therefore, the issue is whether claims to a pure material are unobvious over the prior art. *In re Bergstrom*, 427 F.2d 1394, 166 USPQ 256 (CCPA 1970). Purer forms of known products may be patentable, but the mere purity of a product, by itself, does not render the product unobvious. *Ex parte Gray*, 10 USPQ2d 1922 (Bd. Pat. App. & Inter. 1989).

Factors to be considered in determining whether a purified form of an old product is obvious over the prior art include whether the claimed chemical compound or composition has the same utility as closely related materials in the prior art, and whether the prior art suggests the particular form or structure of the claimed material or suitable methods of obtaining that form or structure. *In re Cofer*, 354 F.2d 664, 148 USPQ 268 (CCPA 1966) (Claims to the free-flowing crystalline form of a compound were held unobvious over references disclosing the viscous liquid form of the same compound because the prior art of record did not suggest the claimed compound in crystalline form or how to obtain such crystals.).".

Asked Questions lists several types of purity standards, both general and specific, that chemical manufacturers adhere to. *See Fisher Scientific International* FAQ, https://www1.fishersci.com/support/ faq/faq_chem.jsp (attached hereto as Exhibit 3). Recognizing that general purity (% assay) is most often what is meant when "purity" is used, Fisher Scientific International recommends that "[w]hen referring to the 'purity' of a product, it is better to use the term 'assay.'" *See id.* at 7.

"General purity" – or assay – is expressed as total weight percent of a principal compound in a sample (*e.g.*, 90% assay). Another connotation of purity, which Appellants refer to as "specific purity," refers to an amount of a particular and typically undesired impurity in the principle compound (*e.g.*, 1% impurity A in the principal compound). Thus, the catalysis chemist and the electrochemist referred to in the BASF FAQ, *supra*, are in Appellants parlance concerned with specific purity – freedom from oxidizable substances for the electrochemist or catalyst poisons for the catalysis chemist. Thus, a sample can have a lower general purity but higher specific purity (*e.g.*, 60% assay, 0.1% impurity A), or vice-versa (*e.g.*, 95% assay, 5% impurity A).

In arguing the rejection, the Office ostensibly relies on the prescript, incorporated in M.P.E.P § 2144.04, that mere purity of a product, by itself, does not render the product unobvious. Appellants vigorously assert that proper application of this prescript in support of a rejection of a claim as *prima facie* obvious requires that "purity" be construed in the sense of "general purity" or assay.

One skilled in the chemical arts is well aware that certain classes of organic compounds, for example dyes and biological stains, have very large extinction coefficients in the visible region of the spectrum. A little bit – a "trace amount" – of such a compound – call it compound

"A" – can go a long way to colorizing a sample of a compound, even a sample having a very high assay. When specific purity – the presence of one or more specific impurities – is the issue, slavish improvement in assay does not create a reasonable expectation that the kineticist's catalyst poison, the electrochemist's oxidizable compound, or the organic chemist's colorizing substance will be removed.

Applying the prescript that a more pure form of a known compound is *prima facie* obvious to reject a claim to the more pure compound – in the specific sense – would be tantamount to denying a claim to one who first removes the electrode-fouling oxidizable material, the catalyst poison, or the colorizing impurity from the respective substance, even such removal (or reduction) resulted in only a *de minims* improvement in assay. *See, e.g., In re Sponnoble*, 405 F.2d 578, 585 (C.C.P.A. 1969) ([A] patentable invention may lie in the discovery of the source of a problem even though the remedy may be obvious once the source of the problem is identified. This is part of the 'subject matter as a whole' which should always be considered in determining the obviousness of an invention under 35 U.S.C. § 103.).

The Office acknowledges that Applicants' claims are not directed to the mere purity of venlafaxine. But the Office rejects the claims alleging that all Applicants have done is to purify venlafaxine. *See* December 28, 2004 Office Action at page 2. Even assuming, *arguendo*, that there *might* be differences in purity between the white crystalline venlafaxine of Applicants' claims and the yellow venlafaxine of undisclosed crystallinity taught by the '555 publication, the Office has not presented any discussion or argument that the differences are differences in assay,

which might support a rejection for *prima facie* obviousness, and not differences in specific purity, which Applicants urge cannot not support such a rejection[2].

3. The Office Erroneously Equates Color and General Purity or Assay

The Office rejects the claims on appeal as *prima facie* obvious. Advisory Action of August 1, 2005. In making the rejection, the Office implicitly equates color and purity, in the sense of general purity or assay, which Applicants have asserted is the only construction of "purity" consistent with the prescript that "mere purity" does not bestow patentability to a claim to a known compound. But color is not a surrogate for purity.

Applicants have already explained why one skilled in the chemical arts knows that purity (assay) and color do not go hand-in-hand. Many practical examples demonstrate this point.

A well-known example of how two compounds with the same general purity can have markedly different colors because of specific impurities is the sapphire-ruby comparison. Both sapphire and ruby are a form of corundum, which "is colorless in its pure state." *AJS Gems Gem Library*, www.ajsgems.com/GemLibrary/Ruby.htm (attached hereto as Exhibit 4). Sapphire is deep blue because of the presence of the impurities iron and titanium. Ruby is traffic-light red because of the presence of chromium as an impurity. For these gems, if the specific color-inducing impurities are not removed, the gems can be purified to the highest assay possible, yet still never be colorless like corundum.

"Different kinds of impurities can produce a wide range of color even in the same crystal structure." Gordon et al., *Crystals*, The Natural History Museum, p. 13 (2004) (attached hereto as Exhibit 5). As illustrated by sapphire and ruby, differences in color do not unquestionably

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[2] Applicants point out that "pure" or "purity" have yet a third connotation in the sense of isolated. A pure (read isolated) form of a compound hitherto only known in mixtures is patentable. *In re Kratz*, 592 F.2d 1169 (CCPA 1979).

depend on general purity (*e.g.*, purifying from 95% to 99%), but can depend on the presence or absence of specific trace impurities. The reasoning applied by the Office would lead to rejection of a claim to blue corundum as *prima facie* obvious in view or red corundum.

That a specific trace impurity, rather than general purity as reflected in an assay, can be responsible for the color of a compound is still further demonstrated by the known but not-yet-fully-understood propensity of paroxetine hydrochloride to exhibit a pink color. According to Avrutov et al., WO 02/102382, which describes a process for preparing paroxetine hydrochloride substantially free of pink-colored compounds, "it is believed that impurities in paroxetine hydrochloride play a role in the color change to pink." WO 02/102382, p. 2, ¶ 1 (attached hereto as Exhibit 6). This publication discusses the effect of a specific impurity on color:

> [One] approach is to measure the degree of **an** impurity identified by a high pressure liquid chromatography ("HPLC") relative retention time ("RRT") of about 1.5. The different UV-spectrum characteristic of **this impurity** has linked the impurity to the development of a pink color. A color change however can occur even if this impurity is present at low levels, suggesting that other impurities may also play a role in the change in color. Purification steps to remove this impurity such as by crystallization, extraction, chromatography or other sepraration procedures are often ineffective.

(emphases added). *Id.*

The chemical company BASF Aktiengesellschaft also addresses the relationship between color and specific impurity content in compounds known as "Ionic Liquids" which, like paroxetine hydrochloride, are susceptible to color change due to the presence of specific color-causing impurities:

> Colored materials are quite often perceived as being impure. In fact, most Ionic Liquids are colorless liquids. However, they tend to become colored especially during prolonged thermal treatment. The good news is that the color persistently stays in the Ionic Liquid and cannot be extracted in any organic product or solvent.

> Currently no one has managed to isolate the colorant because the **quantities are just too low**. It is assumed that oligomers of the imidazole or even radical ions might cause the color.

BASF Aktiengesellschaft FAQ, p. 4 (emphasis added).

4. Crystallinity Alone, and Not General Purity or Assay, may Dictate a Compound's Color

The myth that color is merely a surrogate for purity is further debunked by the fact that crystallinity, not purity, of a compound can be dispositive of its color. A famous example of how the color of a compound is determined by its crystalline form is N-(2'-nitrophenyl)-2-amino-3-cyano-5-methyl thiophene, also known as "ROY." This compound earns its name ROY from the fact that its three crystalline forms dictate whether the compound will be red, orange, or yellow. Smith et al., *Application of Two-Dimensional 13C Solid-State NMR to the Study of Conformational Polymorphism*, J. AM. CHEM. SOC., 11710-11713 (1998) (attached hereto as Exhibit 7). That three crystalline forms of the same compound having the same polymorphic (general) purity exhibit three different colors not because of purity but because of **different crystal structure** is still further demonstration that color is **not** a surrogate of purity.

As the Office acknowledges, Applicants do not claim venlafaxine of a different purity. The Office attempts to circumvent with this acknowledged fact by equating, *sub silentio*, color (in this case lack thereof) and purity (assay). The forgoing discussion amply demonstrates the fallacy of this position.

The Office agrees that the difference between the venlafaxine disclosed in the '555 publication and the white crystalline venlafaxine of the claims on appeal is the color of Applicants' venlafaxine. Because color is not *ipso facto* a proper surrogate for purity in any sense, there is no basis for the Office's assertion that Applicants have done nothing more than to purify venlafaxine.

B. A Stable White Crystalline Material is not *Prima Facie* Obvious over a Yellow Gum that Solidifies upon Standing

Applicants' case is similar to that of *In re Cofer*, 354 F.2d 664 (C.C.P.A. 1966) (attached hereto as Exhibit 8). There, the issue was whether applicant-appellants' claimed product "2,2-B" which was free-flowing and in crystalline form, was obvious in light of cited references disclosing the same compound as a viscous liquid. *In re Cofer*, 354 F.2d at 666. The references cited by the examiner taught that 2,2-B was either "water white" or "amber." *Id.* Appellants pointed to the various advantages of its crystalline product as compared to the prior art such as, for example, "better color, high epoxy content, lower impurity content, and easier to handle . . . ." *Id.* at 666-667. The examiner asserted in the Answer that the appellants' claims "are directed to a more pure form of the disclosed compound which has been made to crystallize and is claimed in its crystalline form as a manufacture." *Id.* at 666.

Reversing the Board's decision which affirmed the obviousness rejection, the court held that the record failed to support the conclusion that those skilled in the art should have known that 2,2-B would exist in crystalline form, or that it would be known how to obtain such crystals. The court stated its reasons as follows:

> There is no explanation in the views of the board or examiner why it should be found from the references or from common knowledge that a person skilled in the art would regard free-flowing crystals of 2,2-B to be obvious. In such circumstances, we are not free to search for speculative reasons that might support the rejection, when it is apparent from those opinions that [the references] were ultimately used only to show that 2,2-B was **known as a viscous liquid**, and not to suggest that the **crystalline** form would also exist.

Id. at 667 (emphases added).

The court found that the Board had "failed to address itself to factors which must be given weight in determining whether the subject matter as a whole would have been obvious,

namely, whether the prior art suggests the **particular structure or form** of the compound or composition as well as suitable **methods of obtaining** that structure or form." *Id.* at 668 (emphases added). In reaching its decision, the court rejected the Board's proposition that "merely changing the form, purity or another characteristic of an old product . . . does not render the claimed product patentable[3]." *Id.* at 667.

Cofer is directly on point. Applicants' claims are directed to a crystalline white venlafaxine. The '555 publication teaches that venlafaxine is instead a yellow gum which, after some undisclosed period of time, eventually "turned slowly in to pale yellow solid." '555 Publication, p. 23, line 24. Applicants are the first to have successfully produced venlafaxine as a white crystalline solid, which, like the 2,2-B in *Cofer* but especially in view of its use in pharmaceuticals, provides significant advantages in color, form, and purity. Applicants have explained in their prior submissions that crystals are typically preferred over gums, which are much more difficult to manipulate in practice, especially in manufacturing. *See, e.g.*, June 27, 2005 Amendment, p. 13. Moreover, the transformation from gum to solid upon sitting for an undisclosed time strongly suggests that the product of the '555 publication is unstable. The Office's position, like that of *Cofer*, is simply that "mere purity of compound, in itself, does not render a substance unobvious." December 28, 2004 Office Action, p. 2.

The same deficiency in *Cofer* is found here, where the cited reference '555 publication does not teach or suggest whiteness or crystallinity of venlafaxine let alone suitable methods of obtaining such venlafaxine. The reference ultimately shows only that venlafaxine was known as

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[3] The Court distinguished from *Ex Parte Hartop*, 139 U.S.P.Q 525, stating that "[n]ecessarily **it is facts appearing in the record, rather than prior decisions** in and of themselves, which must support the legal conclusion of obviousness under 35 USC 103." *Id.* "We see no need to review the cases relied on there save that each case must stand on its own facts." The court further noted that "[t]he cited cases fail to support the broad proposition" advanced by the Board. *Id.* (emphasis added).

a yellow gum that eventually turned into a solid, and cannot be said to suggest that the white crystalline form would also exist. *See In re Cofer*, 354 F.2d at 667. The Office has "failed to address itself to factors which must be given weight in determining whether the subject matter as a whole would have been obvious, namely, whether the prior art suggests the **particular structure or form** of the compound or composition as well as suitable **methods of obtaining** that structure or form." *See id.* at 668 (emphases added).

Cofer rejected the Board's reliance "on the discussion of prior case law in *Hartop*" to reach its conclusion that "the question whether appellant's product had the same or different utility [was] dispositive of the issue here . . . ." *Id.* at 667. The court stressed that whether a chemical compound has the same utility as a closely related material "is only one consideration" in determining obviousness. *Id.* To this end, Applicants respectfully submit that not only is its novel white crystalline compound (and method of its production) not suggested anywhere in the '555 publication, but it further has better utility as a white crystal over a yellow gum. A more advantageous visual appearance which improves the marketability of a product is a utility recognized by the Federal Circuit in assessing patentability. *See Juicy Whip, Inc. v. Orange Bang, Inc.*, 185 F.3d 1364, 1367 (Fed. Cir. 1999). The majority of consumers and pharmaceutical manufacturers would much prefer white crystalline venlafaxine instead of a yellow gum that may later solidify after an unknown amount of time. Therefore, the white crystalline appearance of venlafaxine is an additional utility and improvement over the yellow gum of the '555 publication.

C. The '555 Publication Teaches Away from a White Crystalline Form and the Obviousness Rejection is Improperly Based on Hindsight

At the time of Applicants' invention, the disclosure of the '555 publication that venlafaxine existed as a yellow gum which eventually turned into a solid after an undisclosed

period of time, would have discouraged the skilled artisan from attempting to obtain venlafaxine as a crystalline solid. As mentioned above, the skilled artisan would have recognized that "gums" were inherently unpredictable. One could not have known if or when a transformation of the product disclosed in the '555 publication to a white crystalline solid would occur, or whether the solid would turn back into a gum again. Moreover, Applicants submit that after the solvent is removed in Example 1 of the '555 publication, the yellow venlafaxine gum remains in the reactor vessel, where it slowly solidifies. Because this gum cannot be isolated, it cannot be filtered or processed any further in the hopes of obtaining a different form of venlafaxine, *e.g.* as a white crystal. The '555 publication eviscerates any reasonable expectation that the skilled artisan of the day might have harbored that venlafaxine could exist as a white crystalline solid.

Because the reference teaches venlafaxine (base) as a yellow gum which later unpredictably solidifies, and further because this gum remains in the reactor vessel and is not removed, the skilled artisan seeking to produce a pharmaceutical salt (such as venlafaxine hydrochloride) from the base venlafaxine would be dissuaded from the additional step of isolating the pure base, and would try instead to obtain the hydrochloride salt directly from the gum/solid. Therefore, Applicants assert that the '555 publication teaches away from producing venlafaxine as a white crystal.

The Office also failed to provide a reasonable expectation of success. The mere fact that Applicants, through their diligent efforts in the face of the discouraging teachings of the '555 publication, persevered and discovered white crystalline venlafaxine and its preparation, is not grounds to say, today, that it was obvious this could be done. Such a reliance on hindsight to establish a case of obviousness is improper. *See Hodosh v. Block Drug Co., Inc.*, 786 F.2d 1136, 1143 (Fed. Cir. 1986) ("the references must be viewed without the benefit of hindsight vision

afforded by the claimed invention"). The Office is obligated to provide specific references that teach or suggest the white crystalline form, including methods of obtaining these white crystals, instead of using applicant's disclosure to meet its burden of proof. *See In re Irani*, 57 C.C.P.A. 1109, 1113 (C.C.P.A. 1970). "Even assuming that one skilled in the art could have predicted with reasonable certainty that crystalline [form] could be produced," there must be a showing that "it would also have been obvious **how** this could be achieved." *Id.* at 1113 (emphasis added).

The '555 publication teaches away from a white crystalline form of venlafaxine. The Office has improperly used Applicants' discovery of white crystalline venlafaxine to assert that, because Applicants did it, it was obvious to the skilled artisan of the day to do it and how it could be done.

D. The Examiner has Improperly Taken Official Notice by Equating Color with Purity

Applicants have amply demonstrated, from the foregoing examples, that color is in no way an indicia or "inherent property" of general purity. Moreover, not only is the Office's mistaken presumption factually incorrect, but it is further legally flawed.

The Office's rejection of Applicants' claims is procedurally deficient because it has improperly taken official notice in assuming an inherent nexus between color and general purity and that Applicants' white venlafaxine crystal is simply a purer assay of the yellow solid disclosed in the '555 publication.

The Manual of Patent Examining Procedure (MPEP) proffers extensive guidance "to assist the examiners in determining when it is appropriate to take official notice of facts without supporting documentary evidence or to rely on common knowledge in the art . . . ." *MPEP* § 2144.03. The MPEP clearly states that official notice, unsupported by documentary evidence,

should only be taken where the facts asserted to be well-known are "capable of such **instant and unquestionable demonstration as to defy dispute**." *In re Ahlert*, 57 C.C.P.A. 1023, 1027 (C.C.P.A. 1970) (emphasis added). "If the Patent Office wishes to rest a rejection on **chemical theory, it is its duty to support its case** with adequate evidence of the existence and meaning of that theory." *In re Mills*, 281 F.2d 218, 223-24 (C.C.P.A. 1960) (emphasis added) ("The position of the board is predicated on nothing more than the 'legal presumption' as authority for which it cites [another] case."). "Assertions of technical facts in areas of esoteric technology must always be supported by citation to some reference work recognized as standard in the pertinent art and the appellant given, in the Patent Office, the opportunity to challenge the correctness of the assertion or the notoriety or repute of the cited reference." *In re Ahlert*, 57 C.C.P.A. at 1027.

Apparently, and without a reasoned supporting argument, the Examiner assumes *sub silentio* that color is a surrogate for "purity" in the general assay sense (*e.g.*, 98% to 99% assay), with no regard for the possibility that removal of a specific yellowness-causing impurity led to Applicant's white and crystalline venlafaxine and further without regard to fact that color depends on factors other than assay. In this respect, the Examiner takes official notice, relying on its own knowledge, as to the cause of the yellowness in the venlafaxine in the '555 publication. Whether the lack of color in Applicants' novel venlafaxine is caused by a low general purity or by a specific impurity, the removal of which results in the whiteness of the product or whether color *ipso facto* equates with purity, cannot be said to be "capable of instant and unquestionable demonstration as to defy dispute." *See In re Ahlert*, 424 F.2d at 1091.

Moreover, according to the Code of Federal Regulations:

> When a rejection in an application is based on facts within the personal knowledge of an employee of the Office, the data shall be as specific as possible, and the reference **must be supported, when called for by the applicant, by the affidavit of such**

> **employee**, and such affidavit shall be subject to contradiction or explanation by the affidavits of the applicant and other persons.

37 C.F.R. § 1.104(d)(2) (emphasis added).

Applicants have previously requested that the Examiner provide a reference that teaches or suggests how white crystalline venlafaxine can be obtained, or submit a declaration to support its contention that white crystalline venlafaxine is *prima facie* obvious as a purer assay of the venlafaxine in the '555 publication. *See* June 27, 2005 Amendment, p. 14. However, the Examiner, seeking to rely upon the chemical theory that color is merely an indicia of general purity to establish its *prima facie* case of obviousness, has provided no evidentiary support for the existence and meaning of such a theory. *See In re Mills*, 281 F.2d at 223-24. Instead, the Examiner's rejection is either conclusion based on undisclosed and undocumented knowledge within the ken of the Examiner, or a conclusion "predicated on nothing more than the 'legal presumption' as authority for which it cites" to *Ex parte Gray*, 10 U.S.P.Q.2D (BNA) 1922 (B.P.A.I. 1989). *See In re Mills*, 281 F.2d at 224 ("The 'legal presumption' as here applied by the board precludes making the factual evaluation which a chemist would make in a case such as the present."). "Necessarily it is facts appearing in the record, **rather than prior decisions in and of themselves**, which must support the legal conclusion of obviousness under 35 USC 103." *In re Cofer*, 354 F.2d 664 (C.C.P.A. 1966) (emphasis added).

"The standard of review applied to findings of fact is the 'substantial evidence' standard under the Administrative Procedure Act (APA)." *MPEP* § 2144.03; *In re Lee*, 277 F.3d 1338, 1342-1345 (Fed. Cir. 2002) ("'Common knowledge and common sense,' even if assumed to derive from the agency's expertise, do not substitute for authority when the law requires authority."). Applicants do not dispute that there is substantial technical expertise within the Examining Corps. But the MPEP expressly articulates the guidelines under which official notice

may be taken, stating specifically that when relying upon a chemical theory, the Examiner "must provide evidentiary support for the existence and meaning of that theory." *MPEP* §2144.03(B). Here, the Examiner relies on the "theory" that the color of a compound is a surrogate for the general purity (assay) of the compound. Because the Examiner has provided no evidentiary support, either by way of citation or Examiner's Affidavit, for its bald assertion that there is an inherent nexus between color and purity in the general assay sense, Applicants submit that the "substantial evidence" standard has not been met, and that the Examiner's rejection is therefore improper and should be reversed.

As illustrated above, the presumption that color is an inherent indicia for purity cannot be said to be common knowledge "capable of such instant and unquestionable demonstration as to defy dispute." *See In re Ahlert*, 424 F.2d at 1091. Not only is it pure speculation taken by official notice and not supported by **any** evidence, much less "substantial evidence" as required by the Administrative Procedure Act, but it is also **factually erroneous**, as Applicants have demonstrated with the above examples.

CONCLUSION

Applicants assert that rejection as *prima facie* obvious of a claim allegedly drawn to a more "pure" form of a known compound is appropriate only if "pure" or "purity" denotes purity in the general sense of assay. The Office has erred legally and factually by equating color and general purity in the sense of assay. Applicants have presented theoretical discussion and practical examples showing that one skilled in the art would not have taken a linkage between color and purity as a given.

Because the general purity ↔ color linkage asserted by the Office is far from beyond dispute, it is improper and unlawful for the Office to take official notice of this putative linkage without proffering the required support, which was expressly requested by Applicants.

There are bald assertions but no discussion in the record to support the Office's position that Applicants crystalline white venlafaxine is merely a more pure form [read higher assay form] of the gummy yellow solid of the '555 publication. Because the Office has failed to present a factual or technically sound basis for linking color and assay, the Office fails to make out a case of *prima facie* obviousness against the claims on appeal.

Applicants earnestly argue that nothing in the art of record – alone or in combination with art in the ken of the skilled artisan of the day – teaches or suggests crystalline white venlafaxine or teaches or suggests a method of obtaining it with a reasonable expectation of success. The prospects of obtaining an undesirable yellow gum would suggest to the skilled artisan that they leave venlafaxine alone.

For the foregoing reasons, Claims 1 and 2 cannot be *prima facie* obvious in light of the '555 publication. Claims 95-98, which are product-by-process claims directed to white crystalline venlafaxine, are therefore also non-obvious. Applicants respectfully submit that the rejection of Claims 1, 2 and 95-98 under 35 U.S.C. § 103 is improper and should be reversed.

REQUEST FOR EXTENSION OF TIME

Applicants respectfully request a five-month extension of time in which to file this Appeal Brief in connection with its Notice of Appeal received by the Office on July 1, 2005. The five-month extended period expires on February 1, 2006.

AUTHORIZATION TO DEBIT DEPOSIT ACCOUNT

The Office is further authorized to charge any additional fees required in relation to this paper, or credit any over payments under 37 C.F.R. § 1.16 or § 1.17 to Deposit Account No. **11-0600**, referencing Attorney Docket No. **01662/54902**.

Respectfully submitted,

KENYON & KENYON

Date: Feb. 1, 2006

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CLAIMS APPENDIX

1. A crystalline venlafaxine base wherein the venlafaxine base is in the form of white crystals.

2. A crystalline venlafaxine base according to claim 1, wherein the venlafaxine base has a purity of greater than about 99.3%.

95. White crystalline solid venlafaxine base prepared by a method comprising the steps of:

a) providing a solution of venlafaxine hydrochloride in water,

b) combining the solution of venlafaxine hydrochloride with sodium hydroxide,

c) extracting the combination with an organic solvent to obtain extract,

d) drying the extract,

e) evaporating the extract to obtain a residue,

f) combining the residue with an alkane, and

g) crystallizing venlafaxine base that is a white crystalline solid from the combination of residue and alkane.

96. The white crystalline solid venlafaxine base of claim 95 wherein the organic solvent of step c) is selected from ethyl acetate, heptane, hexane, and mixtures of any of them.

97. The white crystalline solid venlafaxine base of claim 95 having a purity of at least about 98% by weight.

98. The white crystalline solid venlafaxine base of claim 97 having a purity of at least about 99% by weight.

EVIDENCE APPENDIX

1. International publication No. WO 00/32555 (the '555 publication). The '555 publication was cited as prior art in the Office Actions of February 25, 2004 and December 28, 2004.

2. *BASF Aktiengesellschaft* FAQ, http://www2.basf.de/en/intermed/nbd/products/ionicliquids/faq.htm?id=V00-cK1th82Yqbw22XQ#2c. This reference is the basis for Applicants' arguments relating to "purity" and "assay" on p. 10 of the June 27, 2005 Amendment.

3. *Fisher Scientific International*, Frequently Asked Questions, https://www1.fishersci.com/support/faq/faq_chem.jsp. This reference is the basis for Applicants' arguments concerning "purity" and "assay" on p. 10 of the June 27, 2005 Amendment.

4. *AJS Gems Gem Library*, www.ajsgems.com/GemLibrary/Ruby.htm. This was referred to as "Tab A" in Applicants' June 27, 2005 Amendment.

5. Gordon et al., *Crystals*, The Natural History Museum, p. 13 (2004). This was referred to as "Tab A" in Applicants' June 27, 2005 Amendment.

6. International publication No. WO 02/102382. This reference was relied upon by Applicants its June 27, 2005 Amendment.

7. Smith et al., *Application of Two-Dimensional 13C Solid-State NMR to the Study of Conformational Polymorphism*, J. AM. CHEM. SOC., 11710-11713 (1998). This was referred to as "Tab B" in Applicants' June 27, 2005 Amendment.

8. *In re Cofer*, 354 F.2d 664 (C.C.P.A. 1966). This was the primary case was relied upon by Applicants its June 27, 2005 Amendment.

RELATED PROCEEDINGS APPENDIX

Not Applicable.

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(54) Title: DERIVATIVES OF (+)–VENLAFAXINE AND METHODS OF PREPARING AND USING THE SAME

(57) Abstract

Methods of preparing and compositions comprising, derivatives of (+)–venlafaxine are disclosed. Also disclosed are methods of treating and preventing diseases and disorders including, but not limited to, affective disorders such as depression, bipolar and manic disorders, attention deficit disorder, attention deficit disorder with hyperactivity, Parkinson's disease, epilepsy, cerebral function disorders, obesity and weight gain, incontinence, dementia and related disorders.

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DERIVATIVES OF (+)-VENLAFAXINE AND METHODS OF PREPARING AND USING THE SAME

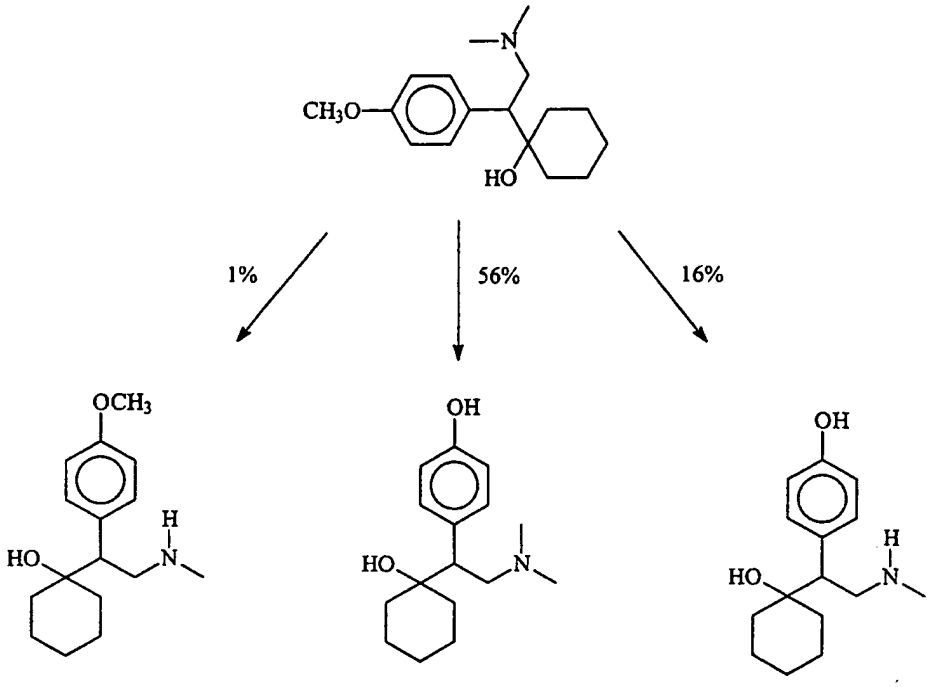
1. FIELD OF INVENTION

The invention relates to optically pure derivatives of (+)-venlafaxine, methods of their synthesis, compositions comprising them, and methods of their use.

2. BACKGROUND OF THE INVENTION

A number of nontricyclic antidepressants have recently been developed that diminish the cardiovascular and anticholinergic liability characteristic of tricyclic antidepressants. Some of these compounds are used as anti-obesity agents and have shown promise in the treatment of cerebral function disorders such as Parkinson's disease and senile dementia. See, e.g., WO 94/00047 and WO 94/00114. The nontricyclic compound venlafaxine, chemically named (±)-1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]-cyclohexanol, is an antidepressant which has been studied extensively and which is described in, for example, U.S. Patent No. 4,761,501 and Pento, J.T. Drugs of the Future 13(9):839-840 (1988). Its hydrochloride salt is currently commercially available in the United States under the trade name Effexor®. Effexor®, which is a racemic mixture of the (+) and (-) enantiomers of venlafaxine, is indicated for the treatment of depression.

Although venlafaxine contains an asymmetric carbon atom and is sold as a racemate, it has been reported that its (-) enantiomer is a more potent inhibitor of norepinephrine synaptosomal uptake while its (+) enantiomer is more selective in inhibiting serotonin uptake. Howell, S.R. et al. Xenobiotica 24(4):315-327 (1994). Furthermore, studies have shown that the ratio of the two isomers' metabolism varies not only among species, but between subjects as well. Klamerus, K.J. et al. J. Clin. Pharmacol. 32:716-724 (1992). In humans, venlafaxine is transformed by a saturable metabolic pathway into two minor metabolites, N-desmethylvenlafaxine and N,O-didesmethylvenlafaxine, and one major metabolite, O-desmethylvenlafaxine, as shown in Scheme I(a):



Scheme I(a)

Klamerus, K.J. et al. J. Clin. Pharmacol. 32:716-724 (1992). All of these metabolites are racemic. *In vitro* studies suggest that O-desmethylvenlafaxine is a more potent inhibitor of norepinephrine and dopamine uptake than the parent compound racemic venlafaxine. Muth, E.A. et al. Drug Develop. Res. 23:191-199 (1991). O-desmethylvenlafaxine has also been reported to have a half-life (t½) of about 10 hours, which is approximately 2.5 times as long as that of venlafaxine. Klamerus, K.J. et al. J. Clin. Pharmacol. 32:716-724 (1992). Studies directed at understanding the activity of O-desmethylvenlafaxine as compared to its parent have been hampered, however, by the metabolic difference between laboratory animals and man in their exposure to venlafaxine. Howell, S.R. et al. Xenobiotica 24(4):315-327 (1994).

Despite the benefits of racemic venlafaxine, it has adverse effects including, but not limited to, sustained hypertension, headache, asthenia, sweating, nausea, constipation, somnolence, dry mouth, dizziness, insomnia, nervousness, anxiety, blurred or blurry vision, and abnormal ejaculation/orgasm or impotence in males. Physicians' Desk Reference pp. 3293-3302 (53rd ed., 1999); see also Sinclair, J. et al. Rev. Contemp. Pharmacother. 9:333-344 (1998). These adverse effects can significantly limit the dose level, frequency, and duration of drug therapy. It would thus be desirable to find a compound with the advantages of venlafaxine while avoiding its disadvantages.

3. SUMMARY OF THE INVENTION

This invention relates to novel pharmaceutical compositions comprising optically pure derivatives of (+)-venlafaxine such as (+)-O-desmethylvenlafaxine. The invention also relates to methods of preparing optically pure derivatives of (+)-venlafaxine with high purity and in high yield, and to methods of treating and preventing diseases and disorders which comprise the administration of one or more optically pure derivatives of (+)-venlafaxine to a human in need of such treatment or prevention.

Methods and compositions of the invention can be used to treat or prevent depression and affective disorders such as, but not limited to, attention deficit disorder and attention deficit disorder with hyperactivity. Methods and compositions of the invention are also useful in treating obesity and weight gain in a human. The invention also encompasses the treatment of cerebral function disorders including, but not limited to, senile dementia, Parkinson's disease, epilepsy, Alzheimer's disease, amnesia/amnestic syndrome, autism and schizophrenia; disorders ameliorated by inhibition of neuronal monamine reuptake; and pain, particularly chronic pain. The invention further encompasses the treatment or prevention of obsessive-compulsive disorder, substance abuse, pre-menstrual syndrome, anxiety, eating disorders and migraines. The invention finally encompasses the treatment or prevention of incontinence in humans.

The compounds and compositions of the invention possess potent activity for treating or preventing the above-described disorders while reducing or avoiding adverse effects including, but not limited to, sustained hypertension, headache, asthenia, sweating, nausea, constipation, somnolence, dry mouth, dizziness, insomnia, nervousness, anxiety, blurred or blurry vision, and abnormal ejaculation/orgasm or impotence in males. In particular, adverse effects associated with the administration of racemic venlafaxine are reduced or avoided by the use of optically pure derivatives of (+)-venlafaxine. Compositions of the invention can also exhibit long half lives as compared to racemic venlafaxine.

Although a variety of pharmaceutical salts, solvates, clatherates and/or hydrates (including anhydrous forms) of the active ingredients disclosed herein are suitable for use in the methods and compositions of the invention, the optically pure derivatives of (+)-venlafaxine are typically prepared as hydrochloride salts, and preferably as the monohydrates.

3.1. DEFINITIONS

As used herein, the terms "venlafaxine" and "(±)-venlafaxine" mean the racemic compound (±)-1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol.

As used herein, the terms "venlafaxine derivative" and "derivative of venlafaxine" encompass, but are not limited to, human metabolites of racemic venlafaxine.

In particular, the terms "venlafaxine derivative" and "derivative of venlafaxine" mean a compound selected from the group that includes, but is not limited to: (±)-N-desmethylvenlafaxine, chemically named (±)-1-[2-(methylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol; (±)-N,N-didesmethylvenlafaxine, chemically named (±)-1-[2-(amino)-1-(4-methoxyphenyl)ethyl]cyclohexanol; (±)-O-desmethylvenlafaxine, chemically named (±)-1-[2-(dimethylamino)-1-(4-phenol)ethyl]cyclohexanol; (±)-N,O-didesmethylvenlafaxine, chemically named (±)-1-[2-(methylamino)-1-(4-phenol)ethyl]cyclohexanol; and (±)-O-desmethyl-N,N-didesmethylvenlafaxine, chemically named chemically named (±)-1-[2-(amino)-1-(4-phenol)ethyl]cyclohexanol.

As used herein, the terms "(+)-venlafaxine derivative" and "derivative of (+)-venlafaxine" encompass, but are not limited to, optically pure human metabolites of (+)-venlafaxine. In particular, the terms "(+)-venlafaxine derivative" and "derivative of (+)-venlafaxine" mean a compound selected from the group that includes, but is not limited to: optically pure (+)-N-desmethylvenlafaxine, chemically named (+)-1-[2-(methylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol; optically pure (+)-N,N-didesmethylvenlafaxine, chemically named (+)-1-[2-(amino)-1-(4-methoxyphenyl)ethyl]cyclohexanol; optically pure (+)-O-desmethylvenlafaxine, chemically named (+)-1-[2-(dimethylamino)-1-(4-phenol)ethyl]cyclohexanol; optically pure (+)-N,O-didesmethylvenlafaxine, chemically named (+)-1-[2-(methylamino)-1-(4-phenol)ethyl]cyclohexanol; and optically pure (+)-O-desmethyl-N,N-didesmethylvenlafaxine, chemically named chemically named (+)-1-[2-(amino)-1-(4-phenol)ethyl]cyclohexanol.

As used herein, the terms "(-)-venlafaxine derivative" and "derivative of (-)-venlafaxine" encompass, but are not limited to, optically pure human metabolites of (-)-venlafaxine. In particular, the terms "(-)-venlafaxine derivative" and "derivative of (-)-venlafaxine" mean a compound selected from the group that includes, but is not limited to: optically pure (-)-N-desmethylvenlafaxine, chemically named (-)-1-[2-(methylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol; optically pure (-)-N,N-didesmethylvenlafaxine, chemically named (-)-1-[2-(amino)-1-(4-methoxyphenyl)ethyl]cyclohexanol; optically pure (-)-O-desmethylvenlafaxine, chemically named (-)-1-[2-(dimethylamino)-1-(4-phenol)ethyl]cyclohexanol; optically pure (-)-N,O-didesmethylvenlafaxine, chemically named (-)-1-[2-(methylamino)-1-(4-phenol)ethyl]cyclohexanol; and optically pure (-)-O-desmethyl-N,N-didesmethylvenlafaxine, chemically named chemically named (-)-1-[2-(amino)-1-(4-phenol)ethyl]cyclohexanol.

As used herein to describe a compound, the term "substantially free of its (-) stereoisomer" means that the compound is made up of a significantly greater proportion of its (+) stereoisomer than of its optical antipode (i.e., its (-) stereoisomer). In a preferred embodiment of the invention, the term "substantially free of its (-) stereoisomer" means that the compound is made up of at least about 90% by weight of its (+) stereoisomer and about

10% by weight or less of its (-) stereoisomer. In a more preferred embodiment of the invention, the term "substantially free of its (-) stereoisomer" means that the compound is made up of at least about 95% by weight of its (+) stereoisomer and about 5% by weight or less of its (-) stereoisomer. In an even more preferred embodiment, the term "substantially free of its (-) stereoisomer" means that the compound is made up of at least about 99% by weight of its (+) stereoisomer and about 1% or less of its (-) stereoisomer. In another preferred embodiment, the term "substantially free of its (-) stereoisomer" means that the compound is made up of nearly 100% by weight of its (+) stereoisomer. The above percentages are based on the total amount of the combined stereoisomers of the compound. The terms "substantially optically pure (+)-venlafaxine derivative," "optically pure (+)-venlafaxine derivative" and "(+) isomer of venlafaxine derivative" all refer to a derivative of (+)-venlafaxine that is substantially free of its (-) stereoisomer.

As used herein, the term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic acids, including inorganic acids and organic acids. Suitable non-toxic acids include inorganic and organic acids such as acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethenesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric acid, p-toluenesulfonic and the like. Particularly preferred are hydrochloric, hydrobromic, phosphoric, and sulfuric acids, and most particularly preferred is the hydrochloride salt.

As used herein, the term "affective disorder" includes depression, attention deficit disorder, attention deficit disorder with hyperactivity, bipolar and manic conditions, and the like. The terms "attention deficit disorder" (ADD) and "attention deficit disorder with hyperactivity" (ADDH), or attention deficit/hyperactivity disorder (AD/HD), are used herein in accordance with the accepted meanings as found in the Diagnostic and Statistical Manual of Mental Disorders, 4th Ed., American Psychiatric Association (1997) (DSM-IV™).

As used herein, the term "a method of treating depression" means relief from the symptoms of depression which include, but are not limited to, changes in mood, feelings of intense sadness, despair, mental slowing, loss of concentration, pessimistic worry, agitation, and self-deprecation. Physical changes may also be relieved, including insomnia, anorexia, weight loss, decreased energy and libido, and abnormal hormonal circadian rhythms.

As used herein, the term "a method for treating obesity or weight gain" means reduction of weight, relief from being overweight, relief from gaining weight, or relief from obesity; all of which are usually due to extensive consumption of food.

As used herein, the term "a method of treating disorders ameliorated by inhibition of neuronal monoamine reuptake" means relief from symptoms of disease states

associated with abnormal neuronal monoamine levels; such symptoms are reduced by way of neuronal monoamine reuptake inhibition. Monoamines, the reuptake of which are inhibited by the compounds or compositions of the present invention, include, but are not limited to, noradrenaline (or norepinephrine), serotonin and dopamine. Disorders treated by neuronal monoamine reuptake inhibition include, but are not limited to, Parkinson's disease and epilepsy.

As used herein, the term "method of treating Parkinson's disease" means relief from the symptoms of Parkinson's disease which include, but are not limited to, slowly increasing disability in purposeful movement, tremors, bradykinesia, rigidity, and a disturbance of posture in humans.

As used herein, the term "a method for treating cerebral function disorders" means relief from the disease states associated with cerebral function disorders involving intellectual deficits which include but are not limited to, senile dementia, Alzheimer's type dementia, memory loss, amnesia/amnestic syndrome, disturbances of consciousness, coma, lowering of attention, speech disorders, Parkinson's disease, Lennox syndrome, autism, hyperkinetic syndrome and schizophrenia. Also within the meaning of cerebral function disorders are disorders caused by cerebrovascular diseases including, but not limited to, cerebral infarction, cerebral bleeding, cerebral arteriosclerosis, cerebral venous thrombosis, head injuries, and the like and where symptoms include disturbances of consciousness, senile dementia, coma, lowering of attention, speech disorders, and the like.

The terms "obsessive-compulsive disorder," "substance abuse," "pre-menstrual syndrome," "anxiety," "eating disorders" and "migraine" are used herein in a manner consistent with their accepted meanings in the art. See, e.g., DSM-IV™. The terms "method of treating or preventing," "method of treating" and "method of preventing" when used in connection with these disorders mean the amelioration, prevention or relief from the symptoms and/or effects associated with these disorders. Without being limited by any theory, the treatment or prevention of certain of these disorders may be related to the activity of the active ingredient(s) as inhibitors of serotonin uptake.

As used herein, the term "a method of treating or preventing incontinence" means prevention of or relief from the symptoms of incontinence including involuntary voiding of feces or urine, and dribbling or leakage or feces or urine which may be due to one or more causes including but not limited to pathology altering sphincter control, loss of cognitive function, overdistention of the bladder, hyper-reflexia and/or involuntary urethral relaxation, weakness of the muscles associated with the bladder or neurologic abnormalities.

4. DETAILED DESCRIPTION OF THE INVENTION

This invention relates to optically pure derivatives of (+)-venlafaxine such as, but not limited to, (+)-O-desmethylvenlafaxine, (+)-N-desmethylvenlafaxine, and (+)-N,O-didesmethylvenlafaxine. This invention further relates to the synthesis of optically pure (+)-venlafaxine derivatives and to compositions (e.g., pharmaceutical compositions) comprising them. The invention also relates to novel uses of the compounds disclosed herein, which constitute improvements over the use of racemic venlafaxine as well as over the optically pure isomers of venlafaxine.

One embodiment of the invention encompasses a method of treating an affective disorder in a human which comprises administering to a human in need of such treatment a therapeutically effective amount of a (+)-venlafaxine derivative, preferably (+)-O-desmethylvenlafaxine, or a pharmaceutically acceptable salt, solvate, or clathrate thereof, substantially free of its (-) stereoisomer. Venlafaxine derivatives, preferably (+)-O-desmethylvenlafaxine, can be used to treat an affective disorder while exhibiting a longer half life than venlafaxine and/or while avoiding or reducing adverse effects that are associated with the administration of venlafaxine.

Another embodiment of the invention encompasses a method of treating weight gain or obesity in a human which comprises administering to a human in need of weight loss or obesity therapy a therapeutically effective amount of a (+)-venlafaxine derivative, preferably (+)-O-desmethylvenlafaxine, or a pharmaceutically acceptable salt, solvate, or clathrate thereof, substantially free of its (-) stereoisomer, said amount being sufficient to reduce or prevent weight gain or obesity. Optically pure (+)-venlafaxine derivatives, preferably (+)-O-desmethylvenlafaxine, can be used to treat weight gain or obesity disorder while exhibiting a longer half life than venlafaxine and/or while avoiding or reducing adverse effects that are associated with the administration of venlafaxine.

Another embodiment of the invention encompasses a method of treating disorders ameliorated by neuronal monoamine reuptake inhibition in a human which comprises administering to a human a therapeutically effective amount of a (+)-venlafaxine derivative, preferably (+)-O-desmethylvenlafaxine, or a pharmaceutically acceptable salt, solvate, or clathrate thereof, substantially free of its (-) stereoisomer, said amount being sufficient to treat such disorders. Disorders which are ameliorated by neuronal monoamine reuptake include, but are not limited to, Parkinson's disease, epilepsy, and depression. The optically pure derivative of (+)-venlafaxine may be used to treat such disorders while avoiding or reducing adverse effects associated with the administration of venlafaxine.

Optically pure, or substantially optically pure, (+)-venlafaxine derivatives, preferably (+)-O-desmethylvenlafaxine, and compositions containing them are also useful in treating cerebral function disorders. Such disorders include, but are not limited to, senile dementia, Alzheimer's type dementia, memory loss, amnesia/amnestic syndrome,

disturbance of consciousness, coma, lowering of attention, speech disorders, Parkinson's disease, Lennox syndrome, autism, hyperkinetic syndrome and schizophrenia. Cerebral function disorders may be induced by factors including, but not limited to, cerebrovascular diseases such as cerebral infarction, cerebral bleeding, cerebral arteriosclerosis, cerebral venous thrombosis, head injuries and the like and where symptoms include disturbances of consciousness, senile dementia, coma, lowering of attention, speech disorders and the like. Thus, the invention encompasses a method of treating cerebral function disorder in a human which comprises administering to a human in need of such therapy a therapeutically effective amount of (+)-venlafaxine derivative, preferably (+)-O-desmethylvenlafaxine, or a pharmaceutically acceptable salt, solvate, or clathrate thereof, substantially free of its (-) stereoisomer. The use of an optically pure (+)-venlafaxine derivative, preferably optically pure (+)-O-desmethylvenlafaxine, is intended to provide an improvement over the use of the parent drug venlafaxine. The optically pure derivatives of the invention are more potent and yet provide an overall improved therapeutic index over venlafaxine.

Another embodiment of the invention encompasses a method of treating pain, including chronic pain, in a human which comprises administering to a human in need of such therapy a therapeutically effective amount of (+)-venlafaxine derivative, preferably (+)-O-desmethylvenlafaxine, or a pharmaceutically acceptable salt, solvate, or clathrate thereof, substantially free of its (-) stereoisomer, said amount being sufficient to alleviate the human's pain.

Another embodiment of the invention encompasses a method of treating an obsessive-compulsive disorder in a human, which comprises administering to a human in need of such therapy a therapeutically effective amount of a (+)-venlafaxine derivative, preferably (+)-O-desmethylvenlafaxine, or a pharmaceutically acceptable salt, solvate, or clathrate thereof, substantially free of its (-) stereoisomer.

Another embodiment of the invention encompasses a method of treating or preventing substance abuse in a human, which comprises administering to a human in need of such therapy a therapeutically effective amount of a (+)-venlafaxine derivative, preferably (+)-O-desmethylvenlafaxine, or a pharmaceutically acceptable salt, solvate, or clathrate thereof, substantially free of its (-) stereoisomer.

Another embodiment of the invention encompasses a method of treating or preventing pre-menstrual syndrome in a human, which comprises administering to a human in need of such therapy a therapeutically effective amount of a (+)-venlafaxine derivative, preferably (+)-O-desmethylvenlafaxine, or a pharmaceutically acceptable salt, solvate, or clathrate thereof, substantially free of its (-) stereoisomer.

Another embodiment of the invention encompasses a method of treating anxiety in a human, which comprises administering to a human in need of such therapy a therapeutically effective amount of a (+)-venlafaxine derivative, preferably

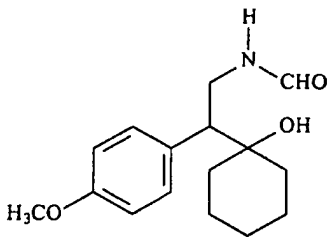
(+)-O-desmethylvenlafaxine, or a pharmaceutically acceptable salt, solvate, or clathrate thereof, substantially free of its (-) stereoisomer.

Another embodiment of the invention encompasses a method of treating an eating disorder in a human, which comprises administering to a human in need of such therapy a therapeutically effective amount of a (+)-venlafaxine derivative, preferably (+)-O-desmethylvenlafaxine, or a pharmaceutically acceptable salt, solvate, or clathrate thereof, substantially free of its (-) stereoisomer.

Another embodiment of the invention encompasses a method of treating or preventing a migraine, or migraine headaches, in a human, which comprises administering to a human in need of such therapy a therapeutically effective amount of a (+)-venlafaxine derivative, preferably (+)-O-desmethylvenlafaxine, or a pharmaceutically acceptable salt, solvate, or clathrate thereof, substantially free of its (-) stereoisomer.

Another embodiment of the invention encompasses a method of treating or preventing incontinence in a human which comprises administering to a human in need of such therapy a therapeutically effective amount of a (+)-venlafaxine derivative, preferably (+)-O-desmethylvenlafaxine, or a pharmaceutically acceptable salt, solvate, or clathrate thereof, substantilly free of its (-) stereoisomer. In particular, a (+)-venlafaxine derivative can be used to treat fecal incontinence, stress urinary incontinence ("SUI"), urinary exertional incontinence, urge incontinence, reflex incontinence, passive incontinence and overflow incontinence. In a preferred embodiments the human is an elder person of an age greater than 50 or a child of an age less than 13. Further, the invention encompasses the treatment of incontinence in patients with either loss of cognitive function, sphincter control or both. The invention is particularly well suited for the treatment or prevention of fecal incontinence and stress urinary incontinence.

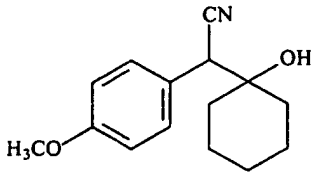
Another embodiment of the invention encompasses a method of preparing (+)-N-desmethylvenlafaxine which comprises contacting a compound of Formula 5:



5

with a reductant for a time and at a temperature sufficient to form (±)-N-desmethylvenlafaxine, and isolating (+)-N-desmethylvenlafaxine therefrom. A preferred reductant is $BH_3 \cdot Me_2S$.

Another embodiment of the invention encompasses a method of preparing (+)-N,N-didesmethylvenlafaxine which comprises contacting a compound of Formula 2:



2

with a reductant for a time and at a temperature sufficient to form (±)-N,N-didesmethylvenlafaxine, and isolating (+)-N,N-didesmethylvenlafaxine therefrom. A preferred reductant is $CoCl_2/NaBH_4$.

Another embodiment of the invention encompasses a method of preparing (+)-O-desmethylvenlafaxine which comprises contacting (+)-venlafaxine with lithium diphenylphosphide for a time and at a temperature sufficient to form (+)-O-desmethylvenlafaxine.

Another embodiment of the invention encompasses a method of preparing (+)-O-desmethylvenlafaxine which comprises contacting (±)-venlafaxine with lithium diphenylphosphide for a time and at a temperature sufficient to form (±)-O-desmethylvenlafaxine, and isolating (+)-O-desmethylvenlafaxine therefrom.

Another embodiment of the invention encompasses substantially pure (+)-O-desmethylvenlafaxine and pharmaceutically acceptable salts, solvates, and clathrates thereof.

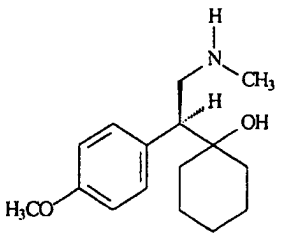
Another embodiment of the invention encompasses substantially pure (+)-N,O-didesmethylvenlafaxine and pharmaceutically acceptable salts, solvates, and clathrates thereof.

Another embodiment of the invention encompasses substantially pure (+)-O-desmethyl-N,N-didesmethylvenlafaxine and pharmaceutically acceptable salts, solvates, and clathrates thereof.

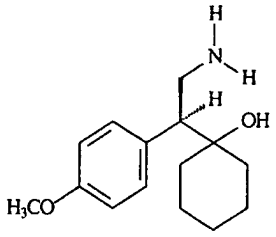
Another embodiment of the invention encompasses (+)-N-desmethylvenlafaxine and pharmaceutically acceptable salts, solvates, and clathrates thereof.

A final embodiment of the invention encompasses (+)-N,N-didesmethylvenlafaxine and pharmaceutically acceptable salts, solvates, and clathrates thereof.

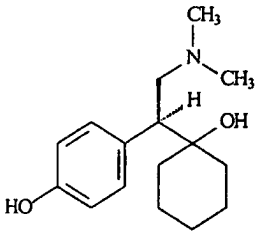
Compounds of the invention, which can be used and prepared as described herein, are shown below in Scheme I(b):



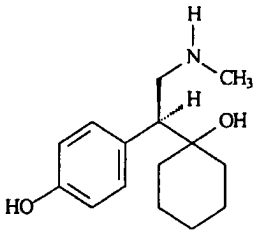
(+)-N-desmethylvenlafaxine



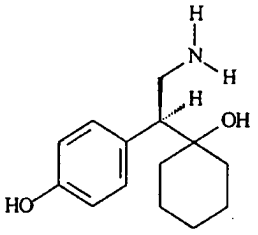
(+)-N,N-didesmethylvenlafaxine



(+)-O-desmethylvenlafaxine



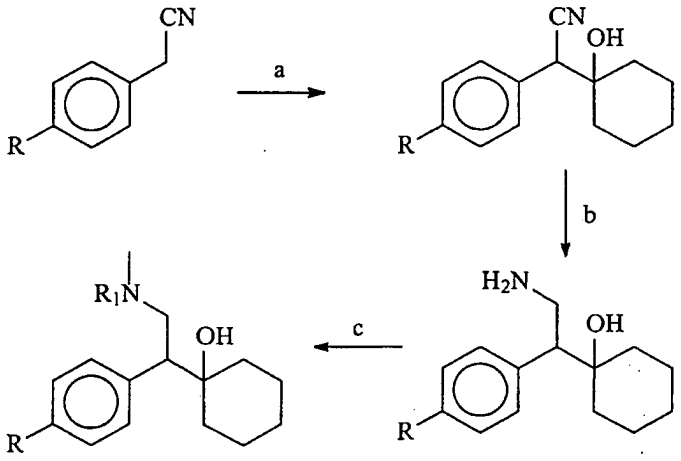
(+)-N,O-didesmethylvenlafaxine



(+)-O-desmethyl-N,N-didesmethylvenlafaxine

Scheme I(b)

The synthesis of some venlafaxine derivatives has been described by Yardley, J.P. et al. J. Med. Chem. 33:2899-2905 (1990), the disclosure of which is hereby incorporated by reference. This method, which may be adapted for the synthesis of the compounds of this invention, is shown in Scheme II:

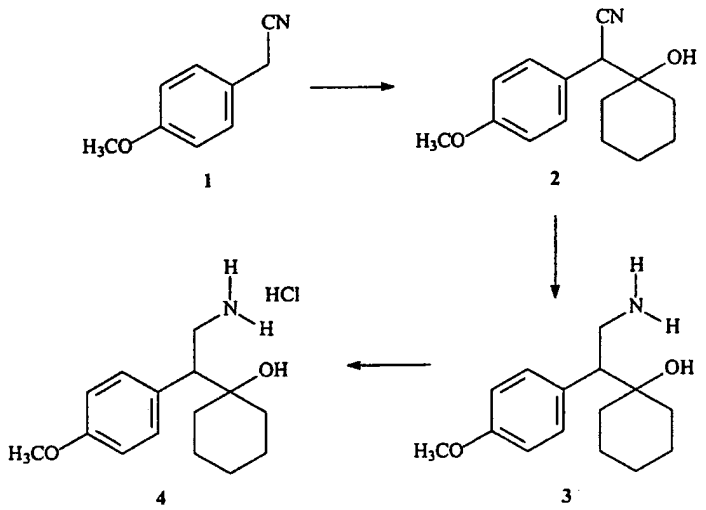


Scheme II

wherein R is methoxy or hydroxy, R_1 is hydrogen or methyl, and the reaction conditions are as follows: (a) LDA in cycloalkanone at -78°C; (b) Rh/Al_2O_3; and (c) HCHO, HCOOH,

H_2O, reflux. The (+) isomer of the racemic final product yielded by step (c) may be isolated by any method known to those skilled in the art, including high performance liquid chromatography (HPLC) and the formation and crystallization of chiral salts. See, e.g., Jacques, J., et al., Enantiomers, Racemates and Resolutions, (Wiley-Interscience, New York, 1981); Wilen, S. H., et al., Tetrahedron 33:2725 (1977); Eliel, E. L. Stereochemistry of Carbon Compounds (McGraw-Hill, NY, 1962); and Wilen, S. H. Tables of Resolving Agents and Optical Resolutions p. 268 (E.L. Eliel, Ed. Univ. of Notre Dame Press, Notre Dame, IN, 1972). As used herein, the term "isolate" encompasses the isolation of a compound from a reaction mixture, the purification of the compound, and the optical resolution of the compound.

In a preferred method of the invention, (+)-N,N-didesmethylvenlafaxine is prepared from (±)-N,N-didesmethylvenlafaxine, which itself is preferably prepared according to the method shown in Scheme III:

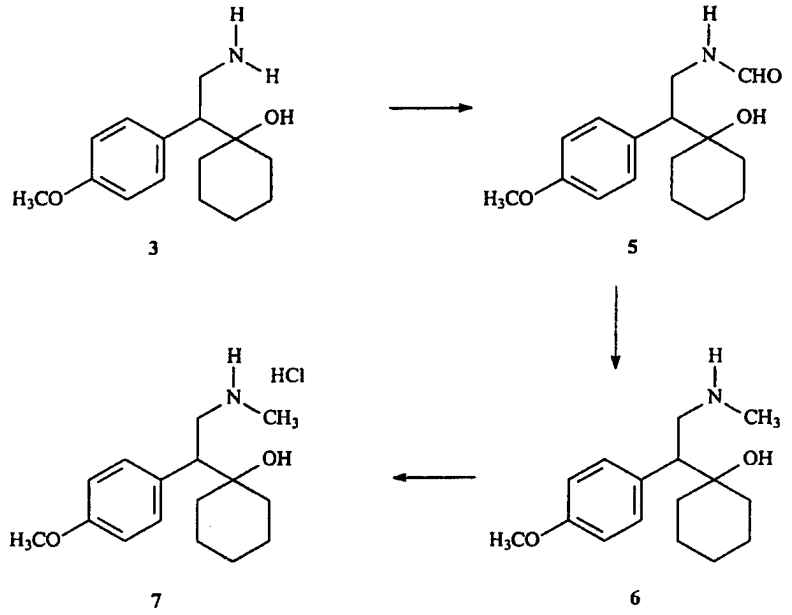


Scheme III

According to this method, cyclohexanone is reacted with compound 1 to provide compound 2. This reaction is preferably done in the presence of a catalyst such as, but not limited to, lithium diisopropylamide (LDA), and in an aprotic solvent such as, but not limited to, THF. The cyano group of compound 2 is subsequently contacted with a reductant to provide compound 3, (±)-N,N-didesmethylvenlafaxine. A preferred reductant is $CoCl_2/NaBH_4$ in methanol, although other reductants known to those skilled in the art can also be used. Salts of (±)-N,N-didesmethylvenlafaxine, such as the HCl salt (compound 4), can then be formed using reaction conditions well known in the art. (+)-N,N-didesmethylvenlafaxine can be isolated from (±)-N,N-didesmethylvenlafaxine using methods known in the art (e.g., by the formation of a chiral salt or using chiral chromatography).

Referring again to Scheme III, (+)-N,N-didesmethylvenlafaxine can alternatively be prepared from the appropriate enantiomer of compound 2. Optically pure enantiomers of compound 2 can be isolated using methods known in the art (e.g., by the formation of a chiral salt or using chiral chromatography).

In another preferred method of the invention, (+)-N-desmethylvenlafaxine is prepared from (±)-N-desmethylvenlafaxine, which itself is prepared from (±)-N,N-didesmethylvenlafaxine according to the method shown in Scheme IV:



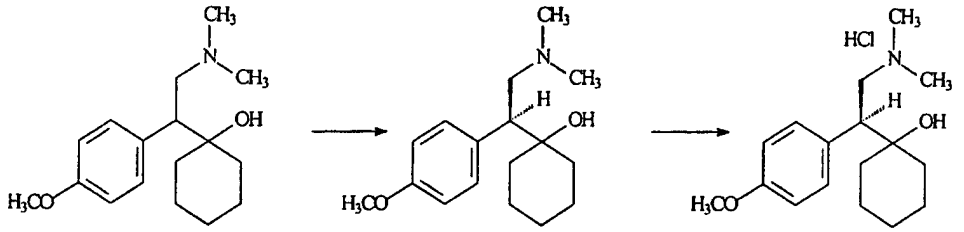
Scheme IV

According to this method, (±)-N,N-didesmethylvenlafaxine (compound 3) is converted to compound 5 using, for example, HCO_2H in a solvent such as, but not limited to, toluene. The aldehyde of compound 5 is subsequently reduced to provide compound 6, (±)-N-desmethylvenlafaxine. A preferred reductant is $BH_3 \cdot Me_2S$ in an aprotic solvent such as, but not limited to, THF. Salts of (±)-N-desmethylvenlafaxine, such as the HCl salt (compound 7), can then be formed using reaction conditions well known in the art. (+)-N-desmethylvenlafaxine can be isolated from (±)-N-desmethylvenlafaxine using methods known in the art (e.g., by the formation of a chiral salt or using chiral chromatography).

Referring again to Scheme IV, (+)-N-desmethylvenlafaxine can alternatively be prepared from the appropriate enantiomers of compounds 3 or 5. Optically pure enantiomers of compounds 3 and 5 can be isolated using methods known in the art (e.g., by the formation of a chiral salt or using chiral chromatography).

It is also possible to prepare the compounds of the invention from racemic venlafaxine, which can be prepared according to methods disclosed, for example, by U.S. Patent No. 4,761,501 and Pento, J.T. Drugs of the Future 13(9):839-840 (1988), both of which are incorporated herein by reference. Optically pure (+)-venlafaxine can be isolated from the racemic mixture by conventional means such as those described above, and then selectively demethylated according to methods known to those skilled in the art. See, e.g., March, J. Advanced Organic Chemistry p. 361 (3rd ed. 1985).

In a preferred method of the invention, optically pure (+)-venlafaxine is isolated from (±)-venlafaxine according to the method shown in Scheme V:

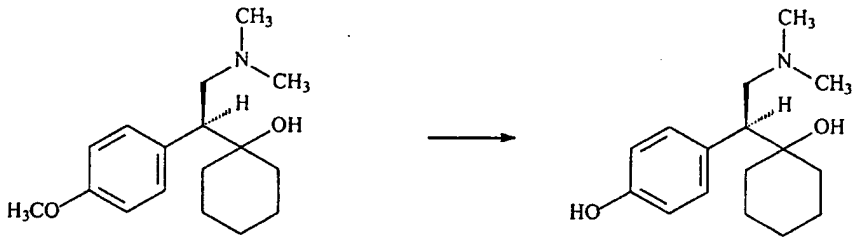


8 9 10

Scheme V

According to this method, (+)-venlafaxine (compound 9) is isolated from (±)-venlafaxine (compound 8) by forming a chiral salt using, for example, di-p-toluoyl-L-tartaric acid. Salts of (+)-venlafaxine, such as the HCl salt (compound 10), can then be formed using reaction conditions well known in the art.

Compounds of the invention are readily prepared from (+)-venlafaxine. For example, in a preferred method of the invention, (+)-O-desmethylvenlafaxine is prepared from (+)-venlafaxine as shown in Scheme VI:

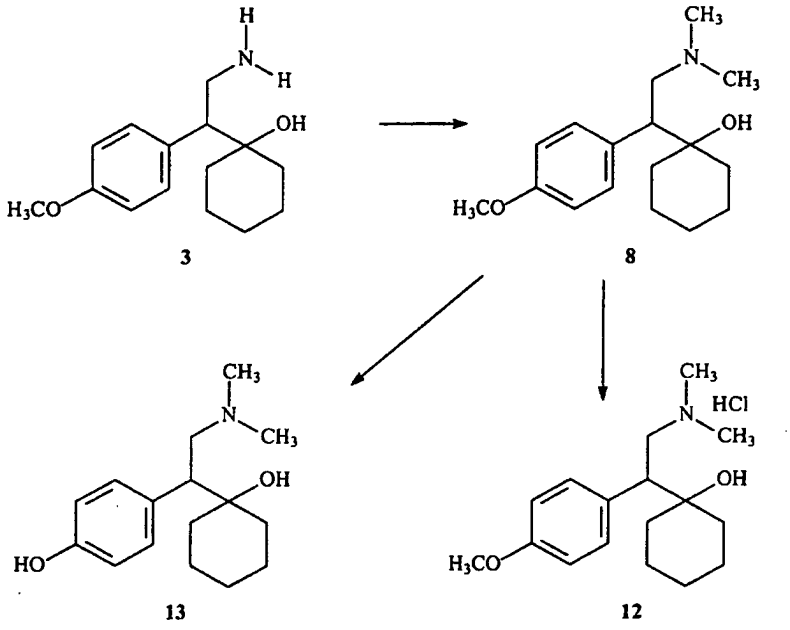


9 11

Scheme VI

According to this method, the methoxy group of (+)-venlafaxine (compound 9) is converted to an alcohol to provide (+)-O-desmethylvenlafaxine (compound 11) using, for example, lithium diphenylphosphide.

Alternative methods of preparing (±)-venlafaxine HCl and (±)-O-desmethyl-venlafaxine, from which optically pure (+)-venlafaxine derivatives can be prepared using methods such as those described herein, are shown in Scheme VII:



Scheme VII

According to Scheme VII, (±)-venlafaxine (compound 8) is prepared by reacting (±)-N,N-didesmethylvenlafaxine (compound 3) with, for example, $HCHO/HCO_2H$. Compound 8 can then be converted to (±)-O-desmethylvenlafaxine (compound 13) using, for example, lithium diphenylphosphide. Alternatively, salts of (±)-venlafaxine, such as the HCl salt (compound 12), can be formed using reaction conditions well known in the art. Optically pure enantiomers of compounds 12 and 13 can be isolated using methods known to those skilled in the art (e.g., by the formation of a chiral salt or using chiral chromatography). Optically pure enantiomers of compounds 12 and 13 can also be prepared according to Scheme VII by beginning with the corresponding optically pure enantiomers of compound 8.

Utilizing the optically pure or substantially optically pure derivatives of (+)-venlafaxine in the treatment and/or mitigation of the conditions described herein results in clearer dose-related definitions of efficacy, diminished adverse effects, and accordingly an improved therapeutic index as compared to venlafaxine itself.

The magnitude of a prophylactic or therapeutic dose of a (+)-venlafaxine derivative (herein also referred to as an "active ingredient"), preferably (+)-O-desmethylvenlafaxine, in the acute or chronic management of a disease will vary with

the severity of the condition to be treated and the route of administration. The dose, and perhaps the dose frequency, will also vary according to age, body weight, response, and the past medical history of the individual patient. In general, the recommended daily dose range for the conditions described herein lie within the range of from about 10 mg to about 1000 mg per day, given as a single once-a-day dose in the morning but preferably as divided doses throughout the day taken with food. Preferably, a daily dose range should be from about 50 mg to about 500 mg per day, more preferably, between about 75 mg and about 350 mg per day. In managing the patient, the therapy should be initiated at a lower dose, perhaps about 50 mg to about 75 mg, and increased if necessary up to about 250 mg to about 325 mg per day as either a single dose or divided doses, depending on the patient's global response. If a dosage is increased, it is preferably done in intervals of about 75 mg separated by at least 4 days.

Because elimination of (+)-venlafaxine derivatives from the bloodstream is dependant on renal and liver function, it is recommended that the total daily dose be reduced by at least 50% in patients with moderate hepatic impairment, and that it be reduced by 25% in patients with mild to moderate renal impairment. For patients undergoing hemodialysis, it is recommended that the total daily dose be reduced by 5% and that the dose be withheld until the dialysis treatment is completed. Because some adverse reactions have been reported for patients who took venlafaxine concurrently with, or shortly after, a monamine oxidase inhibitor, it is recommended that the (+)-venlafaxine derivatives of this invention not be administered to patients currently taking such inhibitors. In general, the concurrent administration of the compounds of this invention with other drugs, particularly other serotonin uptake inhibitors, should be done with care. See, e.g., von Moltke, L.L. et al. Biol. Psychiatry 41:377-380 (1997); and Sinclair, J. et al. Rev. Contemp. Pharmacother. 9:333-344 (1998).

The various terms "said amount being sufficient to alleviate the affective disorder," "said amount being sufficient to alleviate depression," "said amount being sufficient to alleviate attention deficit disorder," "said amount being sufficient to alleviate an obsessive-compulsive disorder", "said amount being sufficient to prevent or alleviate substance abuse", "said amount being sufficient to prevent or alleviate pre-menstrual syndrome", "said amount being sufficient to prevent or alleviate anxiety", "said amount being sufficient to prevent or alleviate an eating disorder", "said amount being sufficient to prevent or alleviate or prevent migraine", "said amount being sufficient to alleviate Parkinson's disease," "said amount being sufficient to alleviate epilepsy," "said amount being sufficient to alleviate obesity or weight gain," "an amount sufficient to achieve weight loss," "said amount being sufficient to bring about weight reduction in a human," "said amount being sufficient to alleviate pain," "said amount being sufficient to alleviate dementia," "said amount sufficient to alleviate said disorders ameliorated by inhibition of

neuronal monoamine reuptake," "said amount is sufficient to alleviate cerebral function disorders" wherein said disorders are selected from the group consisting of senile dementia, Alzheimer's type dementia, memory loss, amnesia/amnestic syndrome, disturbance of consciousness, coma, lowering of attention, speech disorders, Parkinson's disease, Lennox syndrome, autism, hyperkinetic syndrome, schizophrenia, and cerebrovascular diseases, such as cerebral infarction, cerebral bleeding, cerebral arteriosclerosis, cerebral venous thrombosis, head injuries, and the like, "said amount being sufficient to treat or prevent incontinence" wherein said incontinence includes but is not limited to fecal, stress, urinary, urinary exertional, urge, reflex, passive and overflow incontinence, are encompassed by the above described dosage amounts and dose frequency schedule. Similarly, amounts sufficient to alleviate each of the above disorders but insufficient to cause adverse effects associated with venlafaxine are also encompassed by the above described dosage amounts and dose frequency schedule.

Any suitable route of administration can be employed for providing the patient with a therapeutically or prophylactically effective dose of an active ingredient. For example, oral, mucosal (*e.g.*, nasal, sublingual, buccal, rectal, vaginal), parenteral (*e.g.*, intravenous, intramuscular), transdermal, and subcutaneous routes can be employed. Preferred routes of administration include oral, transdermal, and mucosal. Suitable dosage forms for such routes include, but are not limited to, transdermal patches, ophthalmic solutions, sprays, and aerosols. Transdermal compositions can also take the form of creams, lotions, and/or emulsions, which can be included in an appropriate adhesive for application to the skin or can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose. A preferred transdermal dosage form is a "reservoir type" or "matrix type" patch, which is applied to the skin and worn for a specific period of time to permit the penetration of a desired amount of active ingredient. The patch can be replaced with a fresh patch when necessary to provide constant administration of the active ingredient to the patient.

Other dosage forms of the invention include, but are not limited to, tablets, caplets, troches, lozenges, dispersions, suspensions, suppositories, ointments, cataplasms (poultices), pastes, powders, dressings, creams, plasters, solutions, capsules, soft elastic gelatin capsules, and patches.

In practical use, an active ingredient can be combined in an intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier can take a wide variety of forms depending on the form of preparation desired for administration. In preparing the compositions for an oral dosage form, any of the usual pharmaceutical media can be employed as carriers, such as, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents, and the like in the case of oral liquid preparations (such as suspensions, solutions, and

elixirs) or aerosols; or carriers such as starches, sugars, micro-crystalline cellulose, diluents, granulating agents, lubricants, binders, and disintegrating agents can be used in the case of oral solid preparations, preferably without employing the use of lactose. For example, suitable carriers include powders, capsules, and tablets, with the solid oral preparations being preferred over the liquid preparations.

Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit forms, in which case solid pharmaceutical carriers are employed. If desired, tablets can be coated by standard aqueous or nonaqueous techniques.

In addition to the common dosage forms set out above, an active ingredient can also be administered by controlled release means or delivery devices that are well known to those of ordinary skill in the art, such as those described in U.S. Patent Nos.: 3,845,770; 3,916,899; 3,536,809; 3,598,123; and 4,008,719, 5,674,533, 5,059,595, 5,591,767, 5,120,548, 5,073,543, 5,639,476, 5,354,556, and 5,733,566, the disclosures of which are incorporated herein by reference. These dosage forms can be used to provide slow or controlled-release of one or more active ingredients using, for example, hydropropylmethyl cellulose, other polymer matrices, gels, permeable membranes, osmotic systems, multilayer coatings, microparticles, liposomes, or microspheres or a combination thereof to provide the desired release profile in varying proportions. Suitable controlled-release formulations known to those of ordinary skill in the art, including those described herein, can be readily selected for use with the pharmaceutical compositions of the invention. The invention thus encompasses single unit dosage forms suitable for oral administration such as, but not limited to, tablets, capsules, gelcaps, and caplets that are adapted for controlled-release.

All controlled-release pharmaceutical products have a common goal of improving drug therapy over that achieved by their non-controlled counterparts. Ideally, the use of an optimally designed controlled-release preparation in medical treatment is characterized by a minimum of drug substance being employed to cure or control the condition in a minimum amount of time. Advantages of controlled-release formulations include: 1) extended activity of the drug; 2) reduced dosage frequency; and 3) increased patient compliance. In addition, controlled-release formulations can be used to affect the time of onset of action or other characteristics, such as blood levels of the drug, and thus can affect the occurrence of side effects.

Most controlled-release formulations are designed to initially release an amount of drug that promptly produces the desired therapeutic effect, and to gradually and continually release of other amounts of drug to maintain this level of therapeutic effect over an extended period of time. In order to maintain this constant level of drug in the body, the drug must be released from the dosage form at a rate that will replace the amount of drug being metabolized and excreted from the body. Controlled-release of an active ingredient

can be stimulated by various inducers, including, but not limited to, pH, temperature, enzymes, water, or other physiological conditions or compounds.

Pharmaceutical compositions of the invention suitable for oral administration can be presented as discrete dosage forms, such as capsules, cachets, or tablets, or aerosol sprays each containing a predetermined amount of an active ingredient as a powder or in granules, a solution, or a suspension in an aqueous or non-aqueous liquid, an oil-in-water emulsion, or a water-in-oil liquid emulsion. Such dosage forms can be prepared by any of the methods of pharmacy, but all methods include the step of bringing the active ingredient into association with the carrier, which constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation.

For example, a tablet can be prepared by compression or molding, optionally with one or more accessory ingredients. Compressed tablets can be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as powder or granules, optionally mixed with an excipient such as, but not limited to, a binder, a lubricant, an inert diluent, and/or a surface active or dispersing agent. Molded tablets can be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

This invention further encompasses lactose-free pharmaceutical compositions and dosage forms. Lactose is used as an excipient in venlafaxine formulations. *See, e.g., Physician's Desk Reference®* 3294 (53rd ed., 1999). Unlike the parent drug, however, N-demethylated derivatives of (+)-venlafaxine (e.g., (+)-N-desmethylvenlafaxine and (+)-N,N-didesmethylvenlafaxine), are secondary or primary amines and may thus decompose over time when exposed to lactose. Consequently, compositions of the invention that comprise N-demethylated derivatives of (+)-venlafaxine preferably contain little, if any, lactose or other mono- or di-saccharides. As used herein, the term "lactose-free" means that the amount of lactose present, if any, is insufficient to substantially increase the degradation rate of an active ingredient.

Lactose-free compositions of the invention can comprise excipients which are well known in the art and are listed in the USP (XXI)/NF (XVI), which is incorporated herein by reference. In general, lactose-free compositions comprise an active ingredient, a binder/filler, and a lubricant in pharmaceutically compatible and pharmaceutically acceptable amounts. Preferred lactose-free dosage forms comprise an active ingredient, microcrystalline cellulose, pre-gelatinized starch, and magnesium stearate.

This invention further encompasses anhydrous pharmaceutical compositions and dosage forms comprising an active ingredient, since water can facilitate the degradation of some compounds. For example, the addition of water (*e.g.*, 5%) is widely accepted in the

pharmaceutical arts as a means of simulating long-term storage in order to determine characteristics such as shelf-life or the stability of formulations over time. *See, e.g.*, Jens T. Carstensen, *Drug Stability: Principles & Practice*, 2d. Ed., Marcel Dekker, NY, NY, 1995, pp. 379-80. In effect, water and heat accelerate decomposition. Thus the effect of water on a formulation can be of great significance since moisture and/or humidity are commonly encountered during manufacture, handling, packaging, storage, shipment, and use of formulations.

Anhydrous pharmaceutical compositions and dosage forms of the invention can be prepared using anhydrous or low moisture containing ingredients and low moisture or low humidity conditions. Pharmaceutical compositions and dosage forms of the invention which contain lactose are preferably anhydrous if substantial contact with moisture and/or humidity during manufacturing, packaging, and/or storage is expected.

An anhydrous pharmaceutical composition should be prepared and stored such that its anhydrous nature is maintained. Accordingly, anhydrous compositions are preferably packaged using materials known to prevent exposure to water such that they can be included in suitable formulary kits. Examples of suitable packaging include, but are not limited to, hermetically sealed foils, plastic or the like, unit dose containers, blister packs, and strip packs.

In this regard, the invention encompasses a method of preparing a solid pharmaceutical formulation comprising an active ingredient which method comprises admixing under anhydrous or low moisture/humidity conditions the active ingredient and an excipient (*e.g.*, lactose), wherein the ingredients are substantially free of water. The method can further comprise packaging the anhydrous or non-hygroscopic solid formulation under low moisture conditions. By using such conditions, the risk of contact with water is reduced and the degradation of the active ingredient can be prevented or substantially reduced.

Binders suitable for use in pharmaceutical compositions and dosage forms include, but are not limited to, corn starch, potato starch, or other starches, gelatin, natural and synthetic gums such as acacia, sodium alginate, alginic acid, other alginates, powdered tragacanth, guar gum, cellulose and its derivatives (*e.g.*, ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose), polyvinyl pyrrolidone, methyl cellulose, pre-gelatinized starch, hydroxypropyl methyl cellulose, (*e.g.*, Nos. 2208, 2906, 2910), microcrystalline cellulose, and mixtures thereof.

Suitable forms of microcrystalline cellulose include, for example, the materials sold as AVICEL-PH-101, AVICEL-PH-103 AVICEL RC-581, and AVICEL-PH-105 (available from FMC Corporation, American Viscose Division, Avicel Sales, Marcus Hook, PA, U.S.A.). An exemplary suitable binder is a mixture of microcrystalline cellulose

and sodium carboxymethyl cellulose sold as AVICEL RC-581. Suitable anhydrous or low moisture excipients or additives include AVICEL-PH-103™ and Starch 1500 LM.

Examples of suitable fillers for use in the pharmaceutical compositions and dosage forms disclosed herein include, but are not limited to, talc, calcium carbonate (*e.g.*, granules or powder), microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures thereof. The binder/filler in pharmaceutical compositions of the present invention is typically present in about 50 to about 99 weight percent of the pharmaceutical composition.

Disintegrants are used in the compositions of the invention to provide tablets that disintegrate when exposed to an aqueous environment. Too much of a disintegrant will produce tablets which may disintegrate in the bottle. Too little may be insufficient for disintegration to occur and may thus alter the rate and extent of release of the active ingredient(s) from the dosage form. Thus, a sufficient amount of disintegrant that is neither too little nor too much to detrimentally alter the release of the active ingredient(s) should be used to form the dosage forms of the compounds disclosed herein. The amount of disintegrant used varies based upon the type of formulation and mode of administration, and is readily discernible to those of ordinary skill in the art. Typically, about 0.5 to about 15 weight percent of disintegrant, preferably about 1 to about 5 weight percent of disintegrant, can be used in the pharmaceutical composition.

Disintegrants that can be used to form pharmaceutical compositions and dosage forms of the invention include, but are not limited to, agar-agar, alginic acid, calcium carbonate, microcrystalline cellulose, croscarmellose sodium, crospovidone, polacrilin potassium, sodium starch glycolate, potato or tapioca starch, other starches, pre-gelatinized starch, other starches, clays, other algins, other celluloses, gums or mixtures thereof.

Lubricants which can be used to form pharmaceutical compositions and dosage forms of the invention include, but are not limited to, calcium stearate, magnesium stearate, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, stearic acid, sodium lauryl sulfate, talc, hydrogenated vegetable oil (*e.g.*, peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil), zinc stearate, ethyl oleate, ethyl laureate, agar, or mixtures thereof. Additional lubricants include, for example, a syloid silica gel (AEROSIL 200, manufactured by W.R. Grace Co. of Baltimore, MD), a coagulated aerosol of synthetic silica (marketed by Degussa Co. of Plano, Texas), CAB-O-SIL (a pyrogenic silicon dioxide product sold by Cabot Co. of Boston, Mass), or mixtures thereof. A lubricant can optionally be added, typically in an amount of less than about 1 weight percent of the pharmaceutical composition.

Desirably, each tablet contains from about 25 mg to about 150 mg of the active ingredient and each cachet or capsule contains from about 25 mg to about 150 mg of

the active ingredient. Most preferably, the tablet, cachet, or capsule contains either one of three dosages, e.g., about 25 mg, about 50 mg, or about 75 mg of active ingredient (as scored tablets, the preferable dose form).

The invention is further defined by reference to the following examples describing in detail the preparation of the compositions of the invention. It will be apparent to those skilled in the art that many modifications, both to materials and methods, may be practiced without departing from the purpose and interest of this invention.

5. EXAMPLES

As discussed above, at least two different synthetic approaches may be utilized to obtain the compounds of this invention. A first is based upon the isolation of (+)-venlafaxine, followed by selective demethylation. In a second approach, racemic mixtures of venlafaxine derivatives are separated into their optically pure components.

5.1. EXAMPLE 1: Synthesis and Resolution of (+)-Venlafaxine

1-[cyano-(4-methoxyphenyl)methyl]cyclohexanol

A solution of 4-methoxybenzylnitrile (53.5 g, 0.36 mol) in 400 mL THF was cooled to -78°C followed by slow addition of a 2.0 M THF solution of lithium diisopropylamide (200 mL, 0.40 mol) maintaining the reaction temperature below -65°C. The reaction was stirred at -78°C for 30 minutes. Cyclohexanone (39.5 g, 0.40 mol) was added at a rate such that the reaction temperature did not rise above -65°C. After the addition reaction was stirred at -78°C for 2 hours, then was poured into 1 L saturated aqueous NH_4Cl containing ice. The mixture was stirred for 15 minutes and was extracted with ethyl acetate (4 x 200 mL). Combined ethyl acetate layer was washed with water (3x100 mL), brine (1x100 mL) and dried (Na_2SO_4). Ethyl acetate was evaporated *in vacuo* to give colorless solid that was trichurated with hexane. The precipitate was filtered, washed with hexane, dried *in vacuo* to give colorless solid (72.0 g, 80.7% yield). ^1H ($CDCl_3$): 7.30 and 6.90 (q, 4H), 3.80 (s, 3H), 3.75 (s, 1H), 1.55 (m, 10 H); ^{13}C ($CDCl_3$): 159.8, 130.8, 123.8, 120.0, 114.1, 72.9, 55.5, 49.5, 34.9, 25.3, 21.6.

1-[2-amino-1-(4-methoxyphenyl)ethyl]cyclohexanol

A 3-L, three-neck flask equipped with a mechanical stirrer and a thermocouple was charged with 1-[cyano(4-methoxyphenyl)methyl]cyclohexanol (40.0 g, 0.16 mol) and 1 L methanol. To the resulting stirred solution was added cobalt chloride (42.4 g, 0.32 mol) and the reaction was stirred until a clear dark blue solution was obtained. Sodium borohydride (62.0 g, 1.63 mol) was added in small lots maintaining the reaction temperature below 35°C. A dark black precipitate was formed along with vigorous evolution of gas as soon as sodium borohydride was added. After completion of addition

the slurry was stirred at room temperature for 2 hours. TLC examination indicated complete disappearance of the starting material. The reaction was cooled in ice/water and 1 L 3N HCl was added slowly. Reaction temperature was maintained below 25°C. Reaction was stirred for 30 minutes after completion of the addition. Small amount of black precipitate was still observed. Methanol was removed *in vacuo* followed by extraction of the aqueous layer with ethyl acetate (3 x 300 mL). The aqueous layer was cooled in ice/water and was basified (pH paper) by slow addition of concentrated NH_4OH (~600 mL). Reaction temperature was maintained below 25°C. Reaction was extracted with ethyl acetate (4 x 200 mL). Combined ethyl acetate layer was washed with water (3 x 100 mL), brine (1x100 mL), and dried (Na_2SO_4). Ethyl acetate was evaporated *in vacuo* to give yellow gum (34.0 g, 83.6 % yield). ^1H ($CDCl_3$): 7.20 and 6.85 (q, 4H), 3.80 (s, 3H), 3.20 (m, 2H), 2.70 (t, 3H), 2.35 (br s, 3H), 1.40 (m, 10H); ^{13}C ($CDCl_3$): 158.4, 132.6, 130.6, 113.7, 73.7, 56.7, 55.3, 42.4, 37.3, 34.5, 26.0, 21.9.

(±)-Venlafaxine

1-[2-amino-1-(4-methoxyphenyl)ethyl]cyclohexanol (33.0 g, 0.13 mol) was dissolved in 88% formic acid (66.0 g, 55 mL, 1.43 mol) and water (330 mL) followed by addition of 37% aqueous formaldehyde (44.4 g, 41 mL, 1.48 mol). The resulting solution was refluxed for 20 hours, cooled to room temperature and was concentrated to 150 mL, adjusted to pH 2.0 with 3N HCl, and extracted with ethyl acetate (~6 x 50 mL) until pink impurity was removed. The aqueous layer was cooled in ice/water and was basified by slow addition of 50% NaOH. The aqueous layer was extracted with ethyl acetate (3 x 75 mL). Combined ethyl acetate layer was washed with water (3 x 25 mL), brine (1 x 25 mL) and dried (Na_2SO_4). Ethyl acetate was evaporated *in vacuo* to give yellow gum that turned slowly in to pale yellow solid (34.0 g, 92.6 % yield). ^1H ($CDCl_3$): 7.05 and 6.80 (q, 4H), 3.80 (s, 3H), 3.30 (t, 1H), 2.95 (dd, 1H), 2.35 (s, 6H), 2.30 (dd, 1H), 1.30 (m, 10H); ^{13}C ($CDCl_3$): 158.4, 132.9, 130.3, 113.5, 74.4, 61.4, 55.3, 51.8, 45.6, 38.2,31.3,26.2, 21.8, 21.5. MS (277, M+).

(±)-Venlafaxine·HCl Salt

A solution of (±)-venlafaxine (1.0 g, 3.6 mmol) in 100 mL MTBE was cooled to 0°C and 2 mL of 15% HCl in MTBE was added to it. A colorless precipitate was formed. The reaction was stirred at 0°C for 10 minutes. Solid was filtered, washed with MTBE, dried *in vacuo* to give the product as colorless solid (0.700 g, 61.9 % yield). ^1H ($CDCl_3$): 11.40 (s, 1H), 7.15 and 6.85 (q, 4H), 4.05 (d, 1H), 3.80 (s, 3H), 3.35 (t, 1H), 3.20 (m, 2H), 2.80 (s, 3H), 2.60 (s, 3H), 1.30 (m, 10H); ^{13}C ($CDCl_3$): 159.0, 131.4, 130.3, 114.2, 73.7, 60.4, 55.4, 52.7, 45.3, 42.8, 36.7, 31.5, 25.5, 21.7, 21.3. MS (277, M+ for free base). % purity (HPLC): 99.62.

Tartrate Salts of Venlafaxine

To a stirred solution of (±)-venlafaxine (20.0 g, 0.072 mol) in 150 mL ethyl acetate was added a solution of di-p-toluoyl-D-tartaric acid (16.0 g, 0.041 mol) in 120 mL ethyl acetate. Mild exotherm was observed. Colorless solid started precipitating out within 15 minutes. The suspension was stirred at room temperature for 4 hours. The solid was filtered, washed with ethyl acetate, dried *in vacuo* to give (R)-venlafaxine·di-p-toluoyl-D-tartrate salt as colorless solid (18.0 g, 37.6 % yield).

Combined mother liquors from above reaction were washed with ice-cold 1N NaOH (4 x 100 mL), water (3 x 200 mL), brine (1 x 100mL), dried (Na_2SO_4). Ethyl acetate was evaporated *in vacuo* to give colorless solid (10.8 g, 0.039 mol). This solid was dissolved in 75 mL of ethyl acetate and a solution of di-p-toluoyl-L-tartaric acid (11.3 g, 0.029 mol) in 75 mL ethyl acetate was added to it. Colorless solid started precipitating out within 30 minutes. Additional amount of ethyl acetate (50 mL) was added to the slurry and it was stirred overnight at RT. The solid was filtered, washed with ethyl acetate, dried *in vacuo* to give (S)-venlafaxine·di-p-toluoyl-L-tartrate salt as colorless solid (13.0 g, 50.0 % yield).

Crystallization of the Tartrate Salt

(S)-Venlafaxine·di-p-toluoyl-L-tartrate salt (13.0 g, 0.020 mol) was suspended in 250 mL ethyl acetate/ methanol (6:1) and the suspension was warmed to 60°C until a clear solution was obtained. The solution was allowed to cool to room temperature and stirred overnight. Solid was filtered, washed with ethyl acetate/ methanol (6:1), dried. This procedure was repeated two more times. After three crystallizations the product was obtained as colorless solid (5.1 g, 39.2 % yield), e.e. (HPLC): >99.95.

(+)-Venlafaxine

50 mL cold 2N NaOH was added to (S)-(+)-venlafaxine·di-p-toluoyl-L-tartrate salt (4.8 g, 7.24 mmol) and the aqueous layer was extracted with ethyl acetate (3 x 100 mL). Combined ethyl acetate layer was washed with cold 2N NaOH (1 x 25 mL) and water until aqueous wash was neutral. Ethyl acetate layer was dried (Na_2SO_4), ethyl acetate evaporated to give (+)-venlafaxine as colorless solid (2.0 g, quantitative yield), e.e. (HPLC): >99.95. ^1H, ^{13}C and MS data as in (±)-venlafaxine.

(+)-Venlafaxine·HCl Salt

(+)-venlafaxine·HCl salt was prepared from (+)-venlafaxine by following the procedure described for making (±)-venlafaxine·HCl salt.

(+)-Venlafaxine·HCl Salt: colorless solid, $[\alpha]_D$ = +4.4 (c=0.25, EtOH), % purity (HPLC): 99.95, e.e. (HPLC): >99.99. ^1H, ^{13}C and MS data as in (±)-venlafaxine·HCl.

5.2. EXAMPLE 2: Synthesis and Resolution of (+)-O-desmethylvenlafaxine

(±)-O-desmethylvenlafaxine

A solution of diphenylphosphine (3.0 g, 16.1 mmol) in 20 mL THF was cooled to -10°C followed by slow addition of a 1.6 M THF solution of n-BuLi (12.7 mL, 20.2 mmol) at a rate such that reaction temperature did not rise above 0°C. The reaction was stirred at 0°C for 30 minutes. A solution of (±)-venlafaxine (1.0g, 3.6 mmol) in 10 mL THF was added slowly at 0°C. The reaction was stirred at 0°C for 15 minutes and allowed to warm to room temperature and stirred for 1 hour. It was then refluxed overnight. The reaction was cooled to room temperature and was poured slowly into 30 mL cold 3N HCl maintaining the temperature below 15°C. After stirring for 10 minutes, the aqueous layer was extracted with ethyl acetate (3 x 30 mL). The aqueous layer was adjusted to pH 6.8 - 6.9 by slow addition of solid $NaHCO_3$. It was then saturated by adding NaCl and was extracted with ethyl acetate (6 x 30 mL). Combined ethyl acetate layer was dried (Na_2SO_4), ethyl acetate was evaporated *in vacuo* to give colorless solid. The solid was trichurated with cold ethyl acetate, filtered, washed with cold ethyl acetate to give colorless solid (0.700 g, 73.8 % yield). ^1H (DMSO, d_6): 9.30 (br s, 1H), 7.10 and 6.80 (q, 4H), 5.60 (br s, 1H), 3.15 (dd, 1H), 2.88 (t, 1H), 2.50 (dd, 1H), 2.30 (s, 6H), 1.35 (m, 10H); ^{13}C (DMSO, d_6): 155.5, 131.7, 130.1, 114.4, 72.6, 60.4, 51.6, 45.3, 37.2, 32.4, 25.7, 21.2. MS: (264, M+1). % purity (HPLC): 99.9.

(+)-O-desmethylvenlafaxine

(+)-O-desmethylvenlafaxine was prepared from (+)-venlafaxine by following the procedure described above.

(+)-O-desmethylvenlafaxine: colorless solid, $[\alpha]_D = +36.0$ (c=0.25, EtOH), % purity (HPLC): >99.99, e.e. (HPLC): >99.98. ^1H, ^{13}C and MS data as in (±)-O-demethylvenlafaxine.

5.3. EXAMPLE 3: Synthesis of (+)-N-desmethylvenlafaxine

(±)-N-desmethylvenlafaxine

To a solution of 1-[amino (4-methoxyphenyl)ethyl]cyclohexanol (1.0 g, 4.0 mmol) in 8 mL of toluene, 96% formic acid (0.37 g, 8.0 mmol) was added and the reaction was refluxed for 4 hours. It was cooled to room temperature and poured into 40 mL saturated aqueous $NaHCO_3$. Toluene layer was separated and aqueous layer was extracted with toluene (3 x 15 mL). Combined toluene layer was washed with water (3 x 15 mL), brine (1 x 15 mL) and dried (Na_2SO_4). Toluene was evaporated *in vacuo* to give crude N-formyl compound as yellow gum (0.930 g, 83.8 % yield). ^1H ($CDCl_3$): 7.95 (s, 1H), 7.15 and 6.85 (q, 4H), 5.80 (s, 1H), 4.10 (m, 1H), 3.80 (s, 3H), 3.50 (s, 1H), 2.80 (dd, 1H), 1.50 (m, 10H); ^{13}C ($CDCl_3$): 161.4,158.8, 131.0, 130.7, 113.9, 73.0, 55.3, 54.2, 38.1, 36.1, 35.6,

25.6, 21.9, 21.8. (Impurity: 164.5, 129.0, 128.0, 125.0, 56.5, 42.0, 36.5, 35.5). MS (277, M+).

To a solution of crude N-formyl compound (0.585 g, 2.1 mmol) in 6 mL THF was added $BH_3 \cdot Me_2S$ (0.480 g, 0.63 mL of 10 M solution, 6.3 mmol) slowly at 0°C. The reaction was allowed to warm to room temperature and then was refluxed for 5 hours. It was cooled to 0°C and 5 mL of methanol was added very carefully controlling the temperature below 10°C. The reaction was stirred for 10 minutes and volatiles were evaporated off. Residue was partitioned between 3N HCl (20 mL) and ethyl acetate (20 mL). Organic layer was separated and aqueous layer was extracted with ethyl acetate (3 x 15 mL). Aqueous layer was cooled to 0°C and was basified by slow addition of conc. NH_4OH. Aqueous layer was saturated with NaCl and was extracted with ethyl acetate (3 x 20 mL). Combined ethyl acetate layer was dried (Na_2SO_4), ethyl acetate was evaporated *in vacuo* to give colorless oil (0.493 g, 88.8% yield). ^1H ($CDCl_3$): 7.15 and 6.85 (q, 4H), 3.80 (s, 3H), 3.25 (dd, 1H), 2.95 (dd, 1H), 2.82 (dd, 1H), 2.45 (s, 3H), 1.40 (m, 10H); ^{13}C ($CDCl_3$): 158.4, 133.0, 130.5, 113.7, 73.9, 55.4, 53.8, 53.0, 37.8, 36.5, 33.7, 26.0, 21.9.

(±)-N-desmethylvenlafaxine·HCl Salt

To a solution of crude (±)-N-demethylvenlafaxine (0.450 g, 1.7 mmol) in 25 mL MTBE was added 1 mL of 15% HCl in MTBE at 0°C. The resulting slurry was stirred at 0°C for 15 minutes, filtered, solid was washed with MTBE, dried *in vacuo* to give the product as colorless solid (0.380 g, 74.2 % yield). ^1H (CDCl3): 9.10 (br d, 1H), 7.15 and 6.85 (q, 4H), 3.80 (m & s, 4H), 3.35 (dd, 1H), 3.15 (m, 1H), 2.70 (t, 3H), 1.30 (m, 10H); ^{13}C ($CDCl_3$): 159.0, 130.71, 130.4, 114.0, 74.7, 55.4, 52.8, 50.9, 37.0, 34.1,30.9, 25.5, 21.4. %Purity (HPLC): 98.81.

(+)-N-desmethylvenlafaxine

Resolution of optically pure (+)-N-desmethylvenlafaxine may be performed using the methods described herein. If chiral salts are to be used, the amine is preferably protected before formation of the salt. Suitable means of protecting the amines are known to those skilled in the art and include, for example, reaction with phenacylsulfonyl chloride to yield the corresponding sulfonamide, which can be removed after isolation of the optically pure enantiomer with zinc and acetic acid. See, e.g., March, J. Advanced Organic Chemistry p. 445 (3rd ed. 1985).

5.4. EXAMPLE 4: Synthesis of (±)-N,N-didesmethylvenlafaxine·HCl Salt

To a solution of 1-[amino (4-methoxyphenyl)ethyl]cyclohexanol (0.750 g, 3.0 mmol) in 75 mL MTBE was added 2 mL of 15% HCl in MTBE. The reaction was stirred at 0°C for 15 minutes. It was then evaporated to dryness and the residue was

trichurated with MTBE/ hexane (6:4). Solid was filtered, washed with MTBE/ hexane (6:4). The solid was suspended in cold MTBE, filtered, washed with cold MTBE, dried *in vacuo* to give the product as colorless solid (0.450 g, 52.3 % yield). ^{1}H (DMSO, d_6)): 7.80 (br s, 2H), 7.20 and 6.90 (q, 4H), 4.50 (br s, 1H), 3.80 (s, 3H), 3.40 (m, 1H), 3.10 (m, 1H), 2.90 (m, 1H), 1.35 (m, 10H); ^{13}C (DMSO, d_6): 158.3, 130.7, 130.0, 113.5, 71.7, 54.9, 52.6, 36.3, 33.6, 26.8, 25.3, 21.4, 21.1. % Purity (HPLC): 99.3.

5.5. EXAMPLE 5: Synthesis of (±)-O-desmethyl-N,N-didesmethylvenlafaxine

To a solution of diphenylphosphine (22.2 g, 0.12 mol) in 175 ml THF was added a 1.6 M THF solution of n-BuLi (94 mL, 0.15 mol) slowly maintaining the reaction temperature between -10°C to 0°C. After the addition reaction was stirred at 0°C for 30 minutes. A solution of (±)-N,N-didemethylvenlafaxine 13 (5.4 g, 0.021 mol) in 55 mL THF was added slowly at 0°C. The reaction mixture was stirred at 0°C for 30 minutes and allowed to warm to room temperature and stirred at room temperature for 1 hour. It was then refluxed overnight. After cooling the reaction mixture to room temperature, it was poured slowly into 250 mL of 3N HCl while the temperature was maintained below 15°C. After stirring for 30 minutes, the aqueous layer was extracted with methylene chloride (3x200 mL). The aqueous layer was adjusted to pH 6.8-6.9 by slow addition of concentrated NH_4OH at 15°C and was extracted with methylene chloride (3x100 mL). The aqueous layer was then evaporated to dryness to give a colorless solid. This colorless solid was suspended in 400 mL methylene chloride/methanol (7:3) and was stirred for 1 hour. The insolubles were filtered off, washed with methylene chloride/methanol (7:3). The filtrate was evaporated off to give colorless solid. 6.0 g of the colorless solid was chromatographed on silica gel. Elution with methylene chloride/methanol (9:1→8.5:1.5) afforded the product as a colorless solid (1.5 g,). ^{1}H (DMSO, d_6):8.1 (br s, exchangeable, 1H), 6.95 and 6.75 (q, 4H), 4.6 (m, exchangeable, 2H), 3.3 (m, 1H), 2.9 (m, 2H), 1.2 (m, 10H); ^{13}C (DMSO, d_6): 156.8, 130.5, 128.5, 115.2, 72.0, 52.1, 48.6, 36.6, 33.6, 25.6, 21.7, 21.3. %Purity (HPLC): 97.4%.

5.6. EXAMPLE 6: Determination of Potency and Specificity

Several methods useful for the determination of the potency and specificity of the compounds of this invention are disclosed in the literature. See, e.g., Haskins, J.T. et al. Euro. J. Pharmacol. 115:139-146 (1985). Methods that have been found particularly useful are disclosed by Muth, E.A. et al. Biochem. Pharmacol. 35:4493-4497 (1986) and Muth, E.A. et al. Drug Develop. Res. 23:191-199 (1991), both of which are incorporated herein by reference.

5.6.1 Receptor Binding

Determination of receptor binding of the compounds of this invention preferably is performed by the methods disclosed by Muth et al., and using the protocols summarized below in Table I.

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TABLE I. Receptor Binding Protocols

	Ligand			Incubation			
Receptor	^{3}H-Ligand	Molarity (nM)	Specific activity (Ci/mmol)	Buffer	Time	Temp. (°C)	Displacing agent
Dopamine-2	Spiperone	0.3	20-40	* a	10 min	37°	1 mM (+) butaclamol
Adrenergic	WB 4101	0.5	15-30	50 mM Tris-HCl pH 7.7	30 min	25°	10 mM norepinephrine bitartrate
Muscarinic cholinergic	Quinuclindinyl benzilate	0.06	30-60	50 mM Tris-HCl pH 7.7	1 hr	25°	100 mM oxotremorine
Histamine-1	Pyrilamine	2.0	<20	50 mM Phosphate pH 7.5	30 min	25°	10 mM chlorpheniramine maleate
Opiate	Naloxone	1.3	40-60	50 nM Tris-HCl pH 7.4	30 min	0-4°	2 mM morphine

[a]50 mM Tris HCl, 120 mM NaCl, 5 mM KCl, 1 mM $CaCl_2$, 1mM $MgCl_2$, 0.1 % ascorbic acid, 10 mM pargyline HCl, pH 7.1.

The tissue homogenates used are preferably whole brain except cerebellum (histamine-1 and opiate binding), cortex (α_1 adrenergic receptor binding, monoamine uptake); and striatum (dopamine-2 and muscarinic cholinergic receptor binding).

5.6.2 Synaptosomal Uptake Studies

These studies may be performed using the modified methodology of Wood, M.D., and Wyllie, M.G. J. Neurochem. 37:795-797 (1981) as described in Muth et al. Biochem. Pharmacol. 35:4493-4497 (1986). Briefly a P2 pellet is prepared from fresh rat brain tissue by sucrose density gradient centrifugation using a vertical rotor. For uptake studies, all components are dissolved in the following buffer: 135 mM NaCl, 5 mM KCl, 1.2 mM $MgCl_2$, 2.5 mM $CaCl_2$, 10 mM glucose, 1 mM ascorbic acid, 20 mM Tris, pH 7.4, gassed with O_2 for 30 min prior to use. Various concentrations of test drug are preincubated with 0.1 μM [^{3}H]dopamine or 0.1 μM [^{3}H]norepinephrine (130,000 dpm/tube) and 0.1 μM [^{14}C]serotonin (7,500 dpm/tube) in 0.9 ml buffer for 5 min at 37°C. One-tenth milliliter of synaptosomal preparation is added to each tube and incubated for a further 4 min at 37°C. The reaction is then terminated by the addition of 2.5 ml buffer, after which the mixture was filtered under vacuum using cellulose acetate filters (0.45 μM pore size). The filters are then counted in a scintillation counter, and the results are expressed as pmoles uptake/mg protein/min. The IC_{50} values for uptake inhibition are calculated by linear regression of logit [percent of Na^+ -dependent uptake] vs. long [concentration of test drug].

5.6.3. Reversal of Reserpine-Induced Hypothermia

Reversal of reserpine-induced hypothermia in male CF-1 mice (20-25 g., Charles River) may be performed according to an adaptation of the method of Askew, B. Life Sci. 1:725-730 (1963). Test compounds, suspended or solubilized in 0.25% Tween80® in water, are then administered i.p. at several dose levels to male mice (8/dose level) who had been treated 18 hr previously with 45.0 mg/kg reserpine s.c. A vehicle control group is run simultaneously with drug groups. Test compounds, vehicle, and reserpine are administered at a volume of 0.01 ml/g. Reserpine is solubilized by the addition of a small amount (approximately 4 drops) of concentrated acetic acid and then brought to the proper volume by the addition of distilled water. Rectal temperatures are recorded by a Yellow Springs Instruments thermistor probe at a dept of 2 cm. Measurements are taken 18 hr after reserpine pretreatment and at hourly intervals for 3 hr following administration of either test compound or vehicle.

Rectal temperatures for all time periods are subjected to a two-way analysis of variance for repeated measures with subsequent Dunnett's comparison to control values to determine the minimum effective dose (MED) for antagonizing reserpine-induced hypothermia.

5.6.4. Induction of Rat Pineal Noradrenergic Subsensitivity

Suitable rats are male Sprague-Dawley rats (250-300 g, Charles River) which should be maintained in continuous light throughout all experiments so as to attenuate the diurnal fluctuation in beta-adrenergic receptor density in the pineal gland and to maintain a consistent supersensitive response to noradrenergic agonists. Moyer, J.A. et al. Soc. Neurosci. Abstract 10:261 (1984). After 2 days of continuous light exposure, the rats are then injected twice daily with either saline or test compound (10 mg/kg i.p.) for 5 days (total of 9 injections). Another group of rats should receive saline injections twice daily for 4 days followed by a single injection of test compound (10 mg/kg i.p.) on the 5th day. One hour following the final injection of test compound or saline, animals are administered either 0.1% ascorbic acid (controls), or isoproterenol (2 μmol/kg i.p. in 0.1% ascorbic acid). Rats are decapitated 2.5 minutes later, the time at which preliminary experiments have shown that the isoproterenol-induced increases in cyclic AMP levels in pineal glands are maximal. Moyer, J.A. et al. Mol. Pharmacol. 19:187-193 (1981). Pineal glands are removed and frozen on dry ice within 30 seconds to minimize any post-decapitation increase in cAMP concentration.

Prior to radioimmunoassay for cAMP, the pineal glands are placed in 1 ml of ice-cold 2.5% perchloric acid and sonicated for approximately 15 seconds. The sonicate is then centrifuged at 49.000*g* for 15 min at 4°C and then resulting supernatant fluid is removed, neutralized with excess $CaCO_3$, and centrifuged at 12,000*g* for 10 min at 4°C. The cAMP content of the neutralized extract may be measured by a standard radioimmunoassay using ^{125}I-labeled antigen and antiserum (New England Nuclear Corp., Boston, MA). Steiner, A.L. et al. J. Biol. Chem. 247:1106-1113 (1972). All unknown samples should be assayed in duplicate and compared to standard solutions of cAMP prepared in a 2.5% perchloric acid solution that had been neutralized with $CaCO_3$. Results are expressed as pmol cAMP/pineal, and statistical analyses are performed by analysis of variance with subsequent Student-Newman-Keuls tests.

5.6.5. Single Unit Electrophysiology

The firing rates of individual neurons of the locus coeruleus (LC) or dorsal raphe nucleus (DR) in the chloral-hydrate anesthetized rat are measured using single-barreled glass micro-electrodes as previously described for the LC. Haskins, J.T. et al. Eur. J. Pharmacol. 115:139-146 (1985). Using the stereotaxic orientation of Konig, J.F.R., and Klippel, R.A. The rat brain: A stereotaxic atlas of the forebrain and lower parts of the brain stem Baltimore: Williams and Wilkins (1963), the electrode tips should be lowered via a hydraulic microdrive from a point 1.00 mm above the locus coeruleus (AP 2.00 mm caudal to the interaural line and 1.03 mm lateral to midline). Drugs are administered i.v. through a

lateral tail vein cannula. Only one cell should be studied in each rat in order to avoid residual drug effects.

5.7. EXAMPLE 7: Oral Formulation

The pharmaceutical compositions of this invention may be administered in a variety of ways. Oral formulations are of the easiest to administer.

5.7.1. Hard Gelatin Capsule Dosage Forms

Table II provides the ingredients of suitable capsule forms of the pharmaceutical compositions of this invention.

TABLE II

Component	25 mg capsule	50 mg capsule	100 mg capsule
(+)-O-desmethyl-venlafaxine	25	50	100
Microcrystalline Cellulose	90.0	90.0	90.0
Pre-gelatinized Starch	100.3	97.8	82.8
Croscarmellose	7.0	7.0	7.0
Magnesium Stearate	0.2	0.2	0.2

The active ingredient (optically pure (+)-venlafaxine derivative) is sieved and blended with the excipients listed. The mixture is filled into suitably sized two-piece hard gelatin capsules using suitable machinery and methods well known in the art. See Remington's Pharmaceutical Sciences, 16th or 18th Editions, each incorporated herein in its entirety by reference thereto. Other doses may be prepared by altering the fill weight and, if necessary, by changing the capsule size to suit. Any of the stable hard gelatin capsule formulations above may be formed.

5.7.2. Compressed Tablet Dosage Forms

The ingredients of compressed tablet forms of the pharmaceutical compositions of the invention are provided in Table III.

TABLE III. Compressed Tablet Unit Dosage Forms

Component	25 mg capsule	50 mg capsule	100 mg capsule
(+)-O-desmethyl-venlafaxine	25	50	100
Microcrystalline Cellulose	90.0	90.0	90.0
Pre-gelatinized Starch	100.3	97.8	82.8
Croscarmellose	7.0	7.0	7.0
Magnesium Stearate	0.2	0.2	0.2

The active ingredient is sieved through a suitable sieve and blended with the excipients until a uniform blend is formed. The dry blend is screened and blended with the magnesium stearate. The resulting powder blend is then compressed into tablets of desired shape and size. Tablets of other strengths may be prepared by altering the ratio of the active ingredient to the excipient(s) or modifying the table weight.

While the invention has been described with respect to the particular embodiments, it will be apparent to those skilled in the art that various changes and modifications may be made without departing from the spirit and scope of the invention as defined in the claims. Such modifications are also intended to fall within the scope of the appended claims.

THE CLAIMS

What is claimed is:

1. A pharmaceutical composition which comprises (+)-venlafaxine derivative, or a pharmaceutically acceptable salt, solvate, or clathrate thereof, substantially free of its (-) stereoisomer and a pharmaceutically acceptable carrier or excipient.

2. The pharmaceutical composition of claim 1 wherein the (+)-venlafaxine derivative is selected from the group consisting of (+)-O-desmethylvenlafaxine, (+)-N-desmethylvenlafaxine, (+)-N,O-didesmethylvenlafaxine, and (+)-N,N-didesmethylvenlafaxine.

3. The pharmaceutical composition of claim 2 wherein the (+)-venlafaxine derivative is (+)-O-desmethylvenlafaxine or (+)-N,O-didesmethylvenlafaxine.

4. The pharmaceutical composition of claim 1 adapted for intravenous infusion, transdermal delivery, or oral delivery.

5. The pharmaceutical composition of claim 1 wherein the amount of (+)-venlafaxine derivative, or a pharmaceutically acceptable salt thereof, comprises greater than about 90% by weight of the total amount of racemic venlafaxine derivative.

6. The pharmaceutical composition of claim 1 wherein the (+)-venlafaxine derivative comprises a hydrochloride salt thereof.

7. The pharmaceutical composition of claim 1 wherein said pharmaceutically acceptable excipient comprises lactose, croscarmellose sodium, microcrystalline cellulose, pre-gelatinized starch, and magnesium stearate.

8. The pharmaceutical composition of claim 1 wherein said pharmaceutical composition is substantially free of all mono- or di-saccharides.

9. The pharmaceutical composition of claim 8 wherein said pharmaceutical composition is lactose-free.

10. The pharmaceutical composition of claim 1 wherein the (+)-venlafaxine derivative is (+)-O-desmethylvenlafaxine and the excipient comprises lactose.

11. The pharmaceutical composition of claim 10 wherein the excipient further comprises microcrystalline cellulose, pre-gelatinized starch, magnesium stearate, and croscarmellose sodium.

12. A pharmaceutical dosage form which comprises a therapeutically effective amount of (+)-venlafaxine derivative or a pharmaceutically acceptable salt, solvate, or clathrate thereof, substantially free of its (-) stereoisomer, and a pharmaceutically acceptable carrier or excipient.

13. The dosage form of claim 12 wherein said dosage form is a tablet or a capsule.

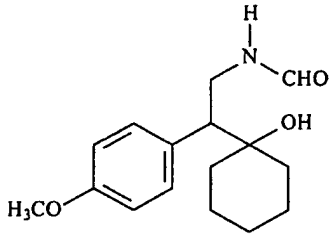
14. The dosage form of claim 12 adapted for intravenous infusion, transdermal delivery, or oral delivery.

15. The dosage form of claim 12 wherein the therapeutically effective amount is from about 10 mg to about 1000 mg.

16. The dosage form of claim 15 wherein the therapeutically effective amount is from about 50 mg to about 500 mg.

17. The dosage form of claim 16 wherein the therapeutically effective amount is from about 75 mg to about 350 mg.

18. A method of preparing (+)-N-desmethylvenlafaxine which comprises contacting a compound of Formula 5:



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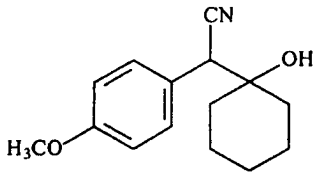
with a reductant for a time and at a temperature sufficient to form (±)-N-desmethylvenlafaxine, and isolating (+)-N-desmethylvenlafaxine therefrom.

19. The method of claim 18 wherein the reductant is $BH_3 \cdot Me_2S$.

20. A method of preparing (+)-N,N-didesmethylvenlafaxine which comprises contacting a compound of Formula 2:



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with a reductant for a time and at a temperature sufficient to form (±)-N,N-didesmethylvenlafaxine, and isolating (+)-N,N-didesmethylvenlafaxine therefrom.

21. The method of claim 20 wherein the reductant is $CoCl_2/NaBH_4$.

22. A method of preparing (+)-O-desmethylvenlafaxine which comprises contacting (±)-venlafaxine with lithium diphenylphosphide for a time and at a temperature sufficient to form (±)-O-desmethylvenlafaxine, and isolating (+)-O-desmethylvenlafaxine therefrom.

23. Substantially pure (+)-O-desmethylvenlafaxine and pharmaceutically acceptable salts, solvates, and clathrates thereof.

24. Substantially pure (+)-N,O-didesmethylvenlafaxine and pharmaceutically acceptable salts, solvates, and clathrates thereof.

25. Substantially pure (+)-O-desmethyl-N,N-didesmethylvenlafaxine and pharmaceutically acceptable salts, solvates, and clathrates thereof.

26. (+)-N-desmethylvenlafaxine and pharmaceutically acceptable salts, solvates, and clathrates thereof.

27. (+)-N,N-didesmethylvenlafaxine and pharmaceutically acceptable salts, solvates, and clathrates thereof.

28. A method of treating an affective disorder in a human which comprises administering to a human in need of such treatment a therapeutically effective amount of a (+)-venlafaxine derivative, or a pharmaceutically acceptable salt, solvate, or clathrate thereof, substantially free of its (-) stereoisomer.

29. The method of treating an affective disorder in a human according to claim 28 in which said amount is sufficient to alleviate the affective disorder but insufficient to cause adverse effects associated with the administration of racemic venlafaxine.

30. The method of claim 28 wherein the affective disorder is selected from the group consisting of depression, attention deficit disorder, and attention deficit disorder with hyperactivity.

31. A method for treating obesity or weight gain in a human which comprises administering to a human in need of a reduction or maintenance in weight a therapeutically effective amount of a (+)-venlafaxine derivative, or a pharmaceutically acceptable salt, solvate, or clathrate thereof, substantially free of its (-) stereoisomer.

32. The method for treating obesity or weight gain in a human according to claim 31 wherein said amount is sufficient to alleviate obesity or weight gain but insufficient to cause the adverse effects associated with administration of racemic venlafaxine.

33. A method of treating disorders ameliorated by inhibition of neuronal monoamine reuptake in a human which comprises administering to a human in need of such treatment a therapeutically effective amount of a (+)-venlafaxine derivative, or a pharmaceutically acceptable salt, solvate, or clathrate thereof, substantially free of its (-) stereoisomer.

34. The method of treating disorders ameliorated by inhibition of neuronal monoamine reuptake in a human according to claim 33 in which said amount is sufficient to alleviate said disorders but insufficient to cause adverse effects associated with administration of racemic venlafaxine.

35. The method of treating disorders ameliorated by inhibition of neuronal monoamine reuptake in a human according to claim 33 wherein said monoamine is dopamine.

36. The method of treating disorders ameliorated by inhibition of neuronal monoamine reuptake in a human according to claim 33 wherein said disorder is Parkinson's disease or epilepsy.

37. A method for treating cerebral function disorders in humans which comprises administering to a human in need of such treatment a therapeutically effective amount of a (+)-venlafaxine derivative, or a pharmaceutically acceptable salt, solvate, or clathrate thereof, substantially free of its (-) stereoisomer.

38. The method for treating cerebral function disorders in a human according to claim 37 wherein said amount is sufficient to alleviate cerebral function disorders but insufficient to cause adverse effects associated with administration of racemic venlafaxine.

39. The method for treating cerebral function disorders in a human according to claim 37 wherein said disorder is caused by a cerebrovascular disease.

40. The method for treating cerebral function disorders in a human according to claim 39 wherein said cerebrovascular disease is selected from the group consisting of cerebral infarction, cerebral bleeding, cerebral arteriosclerosis, cerebral venous thrombosis and head injuries.

41. The method for treating cerebral function disorders in a human according to claim 37 wherein said cerebral function disorder is selected from the group consisting of senile dementia, Alzheimer's type dementia, memory loss and amnesia/amnestic syndrome.

42. A method for treating pain in humans which comprises administering to a human in need of such treatment a therapeutically effective amount of a (+)-venlafaxine derivative, or a pharmaceutically acceptable salt, solvate, or clathrate thereof, substantially free of its (-) stereoisomer.

43. The method for treating pain in a human according to claim 42 wherein said amount is sufficient to alleviate pain but insufficient to cause adverse effects associated with administration of racemic venlafaxine.

44. The method for treating pain in a human according to claim 42 wherein the pain is chronic pain.

45. A method of treating an obsessive-compulsive disorder in a human which comprises administering to a human in need of such treatment a therapeutically effective amount of a (+)-venlafaxine derivative, or a pharmaceutically acceptable salt, solvate, or clathrate thereof, substantially free of its (-) stereoisomer.

46. A method of treating substance abuse in a human which comprises administering to a human in need of such treatment a therapeutically effective amount of a (+)-venlafaxine derivative, or a pharmaceutically acceptable salt, solvate, or clathrate thereof, substantially free of its (-) stereoisomer.

47. A method of treating or preventing pre-menstrual syndrome in a human which comprises administering to a human in need of such treatment or prevention a therapeutically effective amount of a (+)-venlafaxine derivative, or a pharmaceutically acceptable salt, solvate, or clathrate thereof, substantially free of its (-) stereoisomer.

48. A method of treating anxiety in a human, which comprises administering to a human in need of such treatment a therapeutically effective amount of a (+)-venlafaxine derivative, or a pharmaceutically acceptable salt, solvate, or clathrate thereof, substantially free of its (-) stereoisomer.

49. A method of treating an eating disorder in a human, which comprises administering to a human in need of such treatment a therapeutically effective amount of a (+)-venlafaxine derivative, or a pharmaceutically acceptable salt, solvate, or clathrate thereof, substantially free of its (-) stereoisomer.

50. A method of treating or preventing migraine, or migraine headaches, in a human which comprises administering to a human in need of such treatment a therapeutically effective amount of a (+)-venlafaxine derivative, or a pharmaceutically acceptable salt, solvate, or clathrate thereof, substantially free of its (-) stereoisomer.

51. A method for treating or preventing incontinence in a human which comprises administering to a human in need of such treatment a therapeutically effective amount of a (+)-venlafaxine derivative, or a pharmaceutically acceptable salt, solvate, or clathrate thereof, substantially free of its (-) stereoisomer.

52. The method of claim 51 wherein said incontinence is selected from the group consisting fecal incontinence, overflow incontinence, passive incontinence, reflex

incontinence, stress urinary incontinence, urge incontinence, urinary exertional incontinence, and incontinence of urine.

53. The method of claim 28 wherein the (+)-venlafaxine derivative is selected from the group consisting of (+)-O-desmethylvenlafaxine, (+)-N-desmethylvenlafaxine, (+)-N,O-didesmethylvenlafaxine, and (+)-N,N-didesmethylvenlafaxine.

54. The method of claim 53 wherein the (+)-venlafaxine derivative is (+)-O-desmethylvenlafaxine or (+)-N,O-didesmethylvenlafaxine.

55. The method of claim 28 wherein (+)-venlafaxine derivative is administered by intravenous infusion, transdermal delivery, or orally as a tablet or a capsule.

56. The method of claim 28 wherein the amount administered is from about 10 mg to about 1000 mg per day.

57. The method of claim 56 wherein the amount administered is from about 50 mg to about 500 mg per day.

58. The method of claim 57 wherein the amount administered is from about 75 mg to about 350 mg per day.

59. The method of claim 28 wherein the amount of (+)-venlafaxine derivative, or a pharmaceutically acceptable salt, solvate, or clathrate thereof, is greater than approximately 90% by weight of the total amount of racemic venlafaxine derivative.

60. The method of claim 28 wherein the (+)-venlafaxine derivative, or pharmaceutically acceptable salt, solvate, or clathrate thereof, is administered together with a pharmaceutically acceptable carrier.

61. The method of claim 28 wherein the (+)-venlafaxine derivative is administered as a hydrochloride salt.

INTERNATIONAL SEARCH REPORT

Inte. .donal Application No
PCT/US 99/28306

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C215/56 C07C217/64 A61K31/135 A61P25/00 A61P13/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JOHN P. YARDLEY ET AL.: "2-Phenyl-2-(1-hydroxycycloalkyl)ethylamine derivatives: Synthesis and antidepressant activity" JOURNAL OF MEDICINAL CHEMISTRY., vol. 33, no. 10, 1990, pages 2899-2905, XP000891765 WASHINGTON US cited in the application page 2901; page 2904, column 1, last paragraph --- -/--	1,2,4

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 April 2000	09/05/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Rufet, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/28306

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	KLAMERUS K. J. ET AL.: "Introduction of a composite parameter to the pharmacokinetics of Venlafaxine and its active O-desmethyl metabolite" JOURNAL OF CLINICAL PHARMACOLOGY., vol. 32, 1992, pages 716-724, XP000864555 ISSN: 0091-2700 cited in the application the whole document	1,4
A	EP 0 112 669 A (AMERICAN HOME PROD) 4 July 1984 (1984-07-04) abstract; claims 1-14 & US 4 761 501 A cited in the application	1,2
A	EP 0 654 264 A (LILLY CO ELI) 24 May 1995 (1995-05-24) page 2; claims 1,2	1,2
A	US 5 788 986 A (DODMAN NICHOLAS H) 4 August 1998 (1998-08-04) claims 1,6	1,2
A	WO 94 00047 A (SEPRACOR INC) 6 January 1994 (1994-01-06) cited in the application abstract; claims 1-7	1
A	DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US HOWELL S R ET AL.: "Pharmacokinetics of venlafaxine and O-desmethylvenlafaxine in laboratory animals." XP002135579 abstract & XENOBIOTICA, vol. 24, no. 4, 1994, pages 315-327, cited in the application	1
A	DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US MUTH E A ET AL.: "biochemical neurophysiological and behavioral effects of WY-45233 and other identified metabolites of antidepressant venlafaxine" XP002135580 abstract & DRUG DEVELOPMENT RESEARCH, vol. 23, no. 2, 1991, pages 191-199, cited in the application	1

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Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int. ational Application No
PCT/US 99/28306

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A,P	RUDAZ S ET AL.: "Enantioseparation of venlafaxine and O-desmethylvenlafaxine by capillary electrophoresis with mixed cyclodextrins" CHROMATOGRAPHIA, vol. 50, no. 5/6, September 1999 (1999-09), pages 369-372, XP000864541 WIESBADEN, DE ISSN: 0009-5893 abstract	1,2

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 99/28306

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 28-61 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte .tional Application No
PCT/US 99/28306

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0112669 A	04-07-1984	US 4535186 A	13-08-1985
		AT 28628 T	15-08-1987
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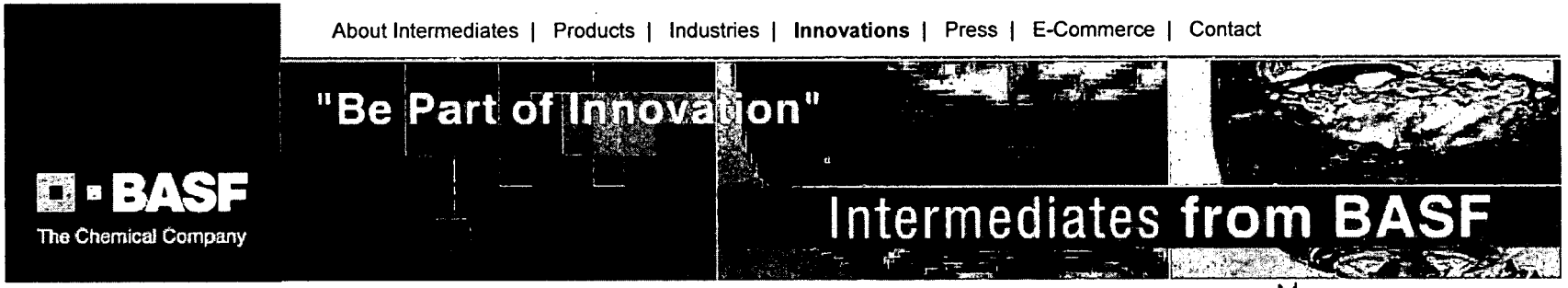

- Intermediates
  - Leading in Intermediates
  - Products
  - Industries
  - E-Commerce
  - New Intermediates
    - Passion for Innovation
    - Innovation News
    - Technologies
    - Products
      - Product Index
      - ChiPros® - Chiral Innovations
      - Ionic Liquids
        - Our Products
        - Our Basil™ Processes
        - Our Team and Contact Data
        - Downloads
        - Awards and Certificates
        - **FAQ**
    - Frequently Asked Questions

Frequently Asked Questions

What are Ionic Liquids?

Ionic liquids are purely ionic, salt-like materials, which are per definition liquid below 100°C. Commonly, they have melting points below room temperature, with some even below 0°C.

News

12/29/05
Formic acid makes airport runways safe for winter take-c and landings

12/21/05
"Ionic Liquids - Solutions for Y Success"

11/30/05
BASF increases prices for BD and derivatives

11/28/05
aMDEA® - Flexible technology gas purification

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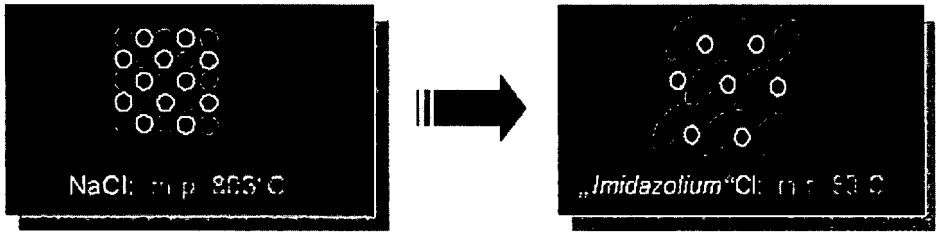
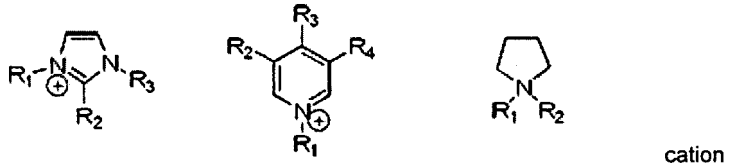
- What would you like to do?

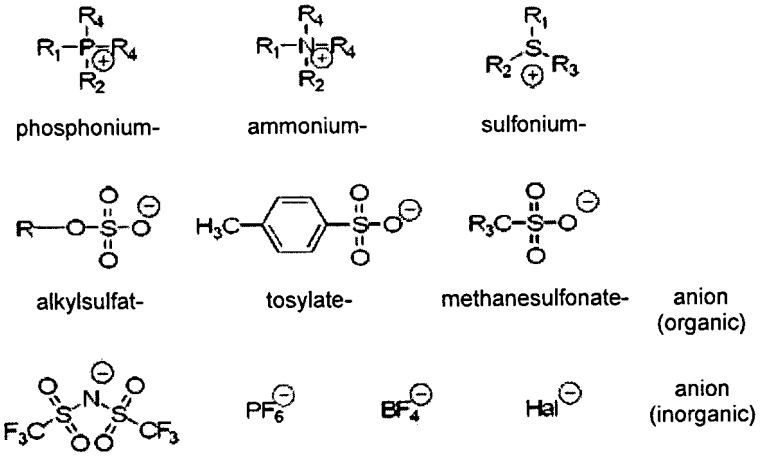
Comparing a typical Ionic Liquid such as 1-ethyl-3-methyl-imidazolium ethylsulfate (m.p. < - 20° C) with a typical inorganic salt, e.g. table salt (NaCl, m.p. 801°C), one can easily see that the Ionic Liquid has a significantly lower symmetry. Consequently, solidification of the Ionic Liquid will take place at lower temperatures. The strong ionic interaction within Ionic Liquids results in a negligible vapor pressure, unless decomposition occurs. It makes the material non-flammable and highly stable thermally, mechanically and electrochemically. Furthermore, it imparts very appealing solvent properties and immiscibility with water or organic solvents that results in biphasic systems.



The cation has a strong impact on the Ionic Liquid's properties and will often define its stability. Furthermore, choice of the anion controls the chemistry and functionality of the Ionic Liquid in general. Although possible combinations of cations and anions can theoretically lead to as many as 1018 Ionic Liquids, a realistic number is magnitudes lower. About 1,000 Ionic Liquids are described in the literature today, and approximately 300 are commercially available. The following illustration shows typical structures that combine organic cations with inorganic or organic anions:



imidazolium- pyridinium- pyrrolidinium- cation (organic)



How pure are Ionic Liquids?

What exactly is purity? Most people would define purity by the actual content of the desired compound expressed in weight percent. This already is not an easy thing to do with Ionic Liquids. As salts they intrinsically consist of two compounds, an cation and an anion. For example a sample of EMIM Cl might contain 5 w% of EMIM HSO_4 as impurity. This means the Ionic Liquid is 100 w% pure in terms of the cation EMIM and 95 w% pure in terms of the anion chloride.

Weight % is only one of many possible definitions of purity. A catalysis chemist would define purity as being free of any coordination species, like halides which deactivate the metal by formation of stable complex compounds. An electrochemist would define purity by having no oxidisable impurities which narrow down the electrochemical window. An engineer might prefer not to have impurities that affect the viscosity and finally the end user will define purity as being free of residual potentially toxic alkylating agents. These examples show, that only the targeted application defines what purity in this case means. In the end Ionic Liquid manufactures do not sell purity, but performance.

Does "technical grade" mean "impure"?

BASF for example provides large scale quantities of Ionic Liquids at a "technical grade". These materials have a certain quality derived from the actual manufacturing process. As an example the parameters for BASIONIC™ LQ01 (EMIM $EtOSO_3$) from a typical ton scale production are

as follows:

Actual content	>99 w%
Acutal color	yellow
Actual content of 1-Methylimidazole	0,2 w%
Actual water content	400 ppm
Actual content of alkylating agent	8 ppm
Actual chloride content	2 ppm

This shows that the initial quality is already very high and "technical grade" does by far not mean "impure". However, as mentioned above, the actual quality has to meet specific needs of the customer. It can turn out that actual content and color for a given application is not relevant, but that the water content must be below 50 ppm. In this case the quality requirements are less challenging regarding actual content, but very demanding regarding water. It not only makes no sense it is even impossible to provide a purity from the beginning that will meet all imaginable future quality issues.

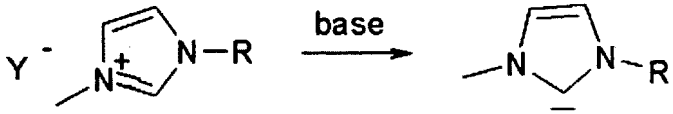
Is the color of Ionic Liquids a problem?

Colored materials are quite often perceived as being impure. In fact, most Ionic Liquids are colorless liquids. However, they tend to become colored especially during prolonged thermal treatment. The good news is that the color persistently stays in the Ionic Liquid and cannot be extracted in any organic product or solvent. Currently no one has managed to isolate the colorant because the quantities are just too low. It is assumed that oligomers of the imidazole or even radical ions might cause the color. For commercial applications the color is usually not a problem, since products are not affected. BASF has been running a pilot plant for an extractive distillation process for 3 months continuously. The color of the Ionic Liquid changed to black, but the performance stayed constant without the need for any purge. During the entire run the product was colorless clear and fully inline with the required specification. For this application it would have been a waste of money to start with a colorless high price Ionic Liquid as the colorless Ionic Liquid would also have turned black under the required high temperatures.

How stable are Ionic Liquids?

Generally Ionic Liquids show remarkably high thermal stabilities of > 200°C. A decomposition pathway of the usually very stable imidazolium-based Ionic Liquid is the back alkylation of the anion.

The back reaction depends on the nucleophilicity of the anion at which temperature this reaction occurs. It has been determined that onset measurements from DSC alone are not suitable to determine the thermal stability. A more valuable indication is provided by TGA analysis which shows the loss of weight due to the distillation of the volatile alkylating agents. For EMIM Acetate the temperature at which 10% loss of weight is observed is for example 215 °C. EMIM Methanesulfonate or EMIM Ethylsulfate show higher thermal stabilities with corresponding decomposition temperatures of 330 °C.
Under basic conditions imidazolium-based Ionic Liquids tend to form carbenes, which can undergo further decomposition, like irreversible disproportionation.



Are Ionic Liquids toxic?

There is no general answer to this question. Since Ionic Liquids can consist of many chemically different types of cations and anions this question has to be answered case by case. The "magic Ionic Liquid" which meets all requirements in toxicity, ecotoxicity, stability and performance simply does not exist. Up to now there is still very limited information available regarding a full toxicological profile of Ionic Liquids. Only recently some valuable data has been published [14]. This data was collected for the notification process of the corresponding Ionic Liquids and represents examples from the most common classes of cations: EMIM, BMIM and ammonium.

	BMIM Cl[1)]	**EMIM $EtOSO_3$**[2)]	**MTEOA $MeOSO_3$**[3)]
Acute oral toxicity	toxic	not harmful	not harmful

Skin irritation	irritant	non-irritant	non-irritant
Eye irritation	irritant	non-irritant	non-irritant
Sensitization	non-sensitizing	non-sensitizing	non-sensitizing
Mutagenicity	non-mutagenic	non-mutagenic	non-mutagenic
Biological degradability	not readily degradable	not readily degradable	readily biodegradable
Toxicity to daphniae	acute toxic	acutely not harmful	acutely not harmful
Toxicity to fish	acutely not harmful	-	acutely not harmful

1) BMIM Cl = 1-Butyl-3-methylimidazolium chloride
2) EMIM EtOSO3 = 1-Ethyl-3-methylimidazolium ethylsulfate
3) MTEOA MeOSO3 = Tris-(2-hydroxyethyl)-methylammonium methylsulfate

These examples show that Ionic Liquids can be toxic as well as completely harmless and biodegradable. However, the harmless Ionic Liquids may not necessarily provide the best performance. In the end a balanced decision between toxicological and performance properties has to be made to gain the best fit to the targeted application. Some Ionic Liquids may only be suitable for being handled by skilled personnel in chemical plants, others for a use closer to the end user will have to be non-toxic and readily biodegradable.

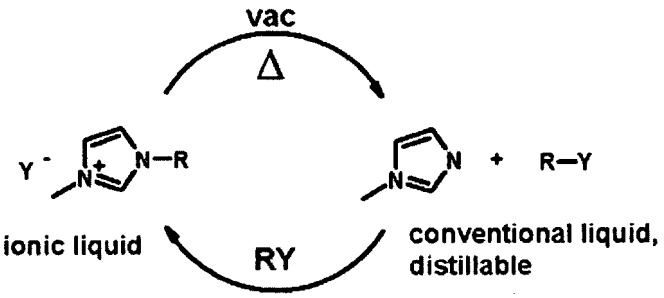
Are Ionic Liquids green?

Besides their technical and economical potential Ionic Liquids are often claimed to be green solvents or green materials. The "greeniness" has often been justified with an important property being that Ionic Liquids have no vapour pressure, hence being not released to the environment by evaporation. Certainly, there might be applications where exactly this property can help to make a particular process greener than a corresponding process with organic solvents. However, this is not necessarily and not generally the case. It might be misleading to assume that non-volatility alone makes a material "green". A more precise approach is to evaluate the whole process from "cradle to grave". This obviously includes the manufacture of raw materials as well as the final product. For example energy consumption in every step has to be considered as well as emissions. BASF is using the eco-efficiency analysis tool in order to evaluate which process from a set of possible alternatives is the most sustainable one. This analysis has been done for the Ionic Liquid based BASIL™ process which was shown to be more sustainable with regard to both, economics and environment. BASIL™ has been awarded with the eco-efficiency

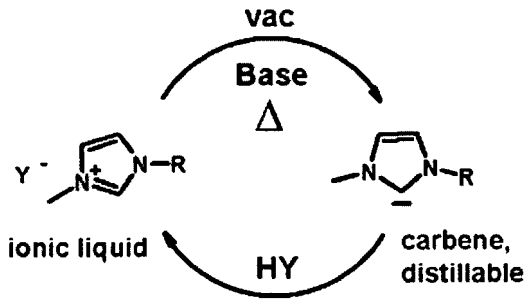
label.

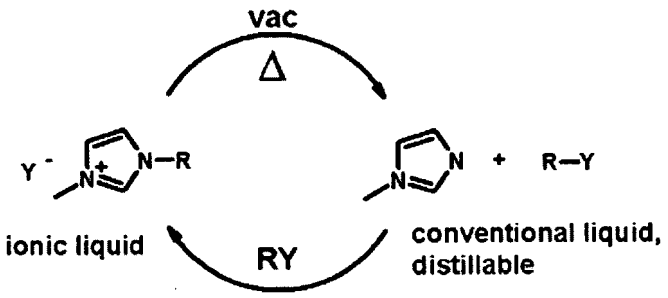
How can Ionic Liquids be recycled?

Recycling of Ionic Liquids is easy, when protonated cations are used. In this case the Ionic Liquids can be switched off by deprotonation. The resulting amine or imidazole is a conventional liquid which can be distilled for recycling or purification purpose.



It is more difficult with the alkylated cations. Apart from a purification or recycling by a liquid-liquid extraction two principal distillations methods haven been reported. The first is the formation of distillable carbenes [WO 01/77081] the second is the back-alkylation of the anion [WO 01/15175; DE 10002420].





Imidazolium cations can be deprotonated by bases to form neutral carbenes. These carbenes are surprisingly stable and can be distilled. The Ionic Liquid can be recycled by further reaction of the carbene with an acid.
This controlled decomposition reaction even allows for a recycling or purification process of the Ionic Liquid. In this case the Ionic Liquid is thermally cleaved. The neutral imidazole and alkylating agent are distilled off, collected and re-reacted.

How can Ionic Liquids be disposed?

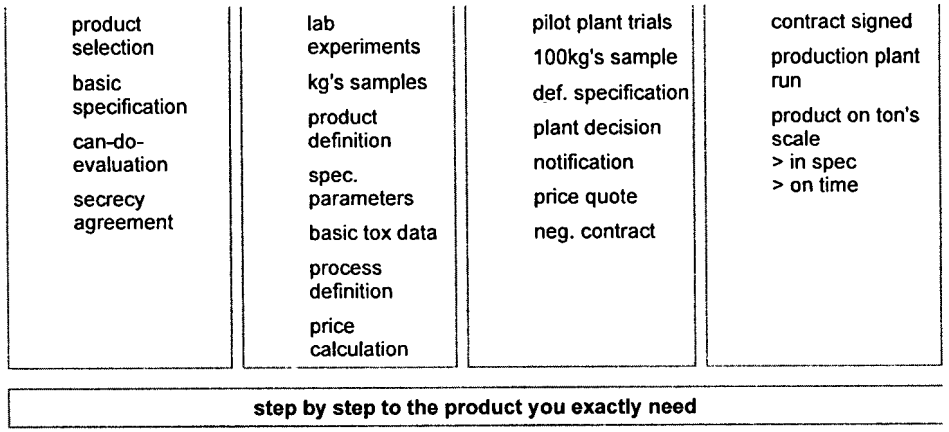
Ionic Liquids are frequently reported as being non-flammable. This is only true up to the temperatures at which decomposition takes place. Some Ionic Liquids already start to decompose at 120°C others are stable up to nearly 400°C. Upon decomposition neutral and volatile molecules are formed which of course can burn. This explains why Ionic Liquids indeed have flash points even if they are usually much higher than 100°C. However, Ionic Liquids can easily be disposed by incineration which is usually done at temperatures of several hundred degrees celsius. At these very high temperatures even the toughest organic Ionic Liquids will give up.

How can I get the Ionic Liquid I really need?

You can either visit web sites and try by yourself to find the right IL or you may ask BASF:

BASF does not offer an extremely broad portfolio of Ionic Liquids - but BASF offers to define specific Ionic Liquids (including specific properties) in discussions with customers

Inquiry **lab trials** **pilot plant** **production**



Why should I think about using Ionic Liquids?

The property profile of Ionic Liquids looks that it may fit to an already realized application where I feel this needs to be improved

The property profile of Ionic Liquids looks that it might enable me to realize an idea I could not realize so far with other materials

I have a problem with one of my applications or processes or I have an idea for a new product or a new process, which I cannot sufficiently realize with what I have so far and I'm questioning myself whether Ionic Liquids may help me

In all these cases, just talk to us, we will be able in a short period of time to give you advice whether IL's may help you and if so we will guide you through the whole development process with our IL expertise.

What prices can be expected for Ionic Liquids?

Prices will mainly depend on the quantity in which specific Ionic Liquids are produced - most of the Ionic Liquids today are manufactured only in kg quantities and therefore are offered at high prices. The price will be also influenced by specific requirements on

specification parameters if these make additional manufacturing steps necessary.

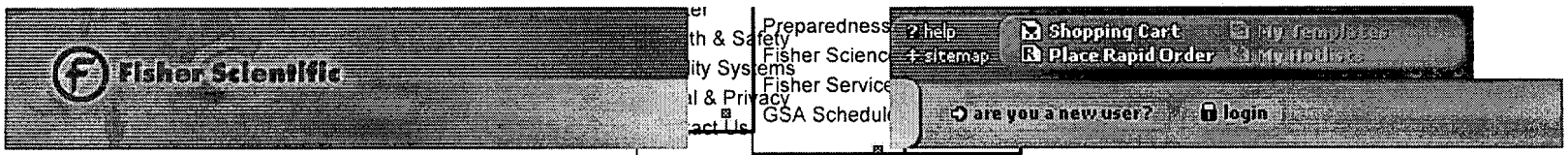
BASF expects to see prices standard quality Ionic Liquids with growing demands in tons quantities below 30€/kg (this expectation is based on first production runs carried our at BASF on a ton scale)

The often mentioned correlation "imidazolium salts are expensive, pyridinium, pyrrolidinium, ammonium, phosphonium etc. salts are less expensive" does not correlate with our calculations. Based on the backward integration within BASF we have internally access to a very broad range of Ionic Liquid precursors enabling us to carry out these calculations with a high degree of accuracy. As it comes to larger quantities, always the performance of the Ionic Liquid will decide which compound is the best as the differentiation in prices will be only small.

Which Ionic Liquid should I use?

In many publications today - for several reasons - most often imidazolium salts are mentioned as the preferred Ionic Liquid materials. From our experience imidazolium salts indeed offer a lot of advantages and we therefore also set a focus on these. Nevertheless, with each application we evaluate, we also check other opportunities, targeting to identify the optimal Ionic Liquid showing the best fit between the properties and the requirements in the desired application.

The discussion on potential prices for Ionic Liquids are often limited to statements like imidazolium salts expensive and ammonium salts cheap. From our point of view there is not really a basis for these statements as we have not seen big differences in our cost calculations for Ionic Liquids with different cations. On the other side the anion should not be underestimated as in many cases the anion will define the performance of the Ionic Liquid as well as the price (for example in electrochemical applications, where often fluorinated anions are required).



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FAQS

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FAQ

General Information

How can I view Material Safety Data Sheets through your Web site?
How can I receive Certificate of Analysis?
Why don't all chemicals have an "outdate" to indicate shelf life?
At which temperature should I store my chemicals?
Are Fisher pH Buffers traceable to NIST?

Chemical Grades

Which purity grades are Fisher chemicals manufactured to meet?

Acronyms

FAQs on Alcohol

Is there a difference between alcohol and ethanol?
What is the difference between pure and purity?
What is Anhydrous Alcohol?
What is Specially Denatured Alcohol (SDA)?
What is Completely Denatured Alcohol?
What is the difference between natural and synthetic?
What is the difference between 190-proof and 200-proof?
What is the difference between Taxable and Nontaxable Alcohol?
Is there a difference between "Proof Gallon" and "Wine Gallon?"
Can pure ethanol be purchased without a BATF permit?
Can specially denatured alcohol be bought without a BATF permit?
I need custom packaging. Can you do this?
I need chemicals that comply with international testing requirements. Can Fisher supply these items to me?

Q. How can I view Material Safety Data Sheets through your web site?

A. MSDSs for chemicals and reagents manufactured by Fisher can be easily viewed and printed from our web site. Click here for detailed instructions.

Q. How can I receive Certificate of Analysis?

A.You can download a Certificate of Analysis from this site. Click here for details. You can also use Fisher's Fax-on-Demand System to request Certificates of Analysis (C of A) for Fisher chemicals and Acros organics products. The system is available 24 hours a day, 7 days a week.

1. Call 1-201-703-3165:
Just listen to the recorded message and follow the directions.
2. When requesting C of As, have available:
The first six digits of the lot number shown on the label of the chemical you're inquiring about (lot numbers begin with two digits representing the year, such as 971234) and the first letter of the product's catalog number. Also supply your fax number.
3. Enter information
Follow the instructions and enter your request using your touch-tone telephone. Enter letters by pressing the corresponding number on your telephone keypad.
4. Receive your certificate(s)
Your certificate(s) will be faxed promptly to the number you entered in Step 3—usually within 30 minutes. If your fax line is busy, our system will redial repeatedly and only terminate the transmission if it cannot get through in those attempts. If you don't receive a response within 30 minutes, place your request again.

Q. Why don't all chemicals have an "outdate" to indicate shelf life?

A. Some of the chemicals from Fisher may not have an outdate simply because those materials do not decompose under normal storage conditions. They should have an indefinite shelf life if they are not contaminated or adulterated. If the product you purchase from Fisher has a known instability, an outdate will be noted on the label. Unless otherwise specified, the outdate will be the last day of the month indicated on the label.

It is good Chemical Practice, however, not to keep chemicals beyond 3 to 5 years. Over extended periods of time, conditions beyond your direct control could cause degradation of even stable compounds. Generally, the first two digits of the lot number will indicate the year of manufacture.

Q. At which temperature should I store my chemicals?

A. Storage conditions for all Fisher chemicals would be room temperature unless otherwise stated on the label.

Q. Are Fisher pH Buffers traceable to NIST?

A. Yes, our buffer solutions — manufactured by FisherChemical — are directly traceable to NIST. For traceability of specific product lots to specific standard lots, fax your request to 201-703-3159.

Q. Which purity grades are Fisher chemicals manufactured to meet?

A. Fisher chemicals are available in a wide range of purity grades to meet all applications.

grade	definition	application	certificate of analysis

GC Resolv*	Solvents with the highest purity and lot-to-lot consistency. Free of contaminants to ppb level, including those listed in the Contract Laboratory Program Target Compound List. Grade meets ACS specifications. Chromatogram available.	Gas chromatography	Provided with each shipment
OPTIMA*	Acids and solvents of extremely high purity. Acids are analyzed for 72 metals by ICP/MS; impurity levels in ppt. Solvent impurity levels in ppm. UV absorbance curves and sample chromatograms available on request.	HPLC, GC, plasma/ICP, spectrophotometry, and pesticide residue analysis	Provided with each shipment
HPLC	Solvents manufactured specifically for use with HPLC instruments. Grade meets all ACS specifications. Submicron filtered.	HPLC and spectrophotometry procedures	Available on request
Pesticide	Solvents for use in analysis of pesticide residue. Pesticide grade meets or exceeds ACS standards of purity for pesticide residue analysis.	GC with electron capture detector (ECD)	Available on request
Spectranalyzed*	Solvents for use in spectrophotometry. Grade meets all ACS specifications. Actual lot analysis is printed on label.	Available on request	Available on request
Biotechnology	Solvents and reagents that have been specially purified and assayed for biotechnology applications.	Electrophoresis, molecular biology, sequencing, and peptide and oligonucleotide synthesis	Available on request
Scintanalyzed*	Solvents, fluors, and prepared cocktails for liquid scintillation counting. Includes non-flammable, nontoxic, biodegradable ScintiSafe* cocktails.	Liquid scintillation counting	Available on request
Electronic	Solvents manufactured to ensure low levels of metal contamination. Grade meets Semiconductor Equipment and Materials Institute (SEMI) requirements. Actual lot analysis is printed on the label.	Electronics and circuit board manufacturing.	Available on request
TraceMetal	Acids manufactured to achieve low metal contamination measurable in ppm to ppb range. Each lot is analyzed for more than 30 metals by ICP/MS.	Primarily used in digestion of samples prior to instrument (ICP) analysis	Provided with each shipment
Certified ACS Plus	Acids which, in addition to meeting or exceeding the latest specifications of the ACS, are analyzed for more than 16 metals. Actual lot analysis is printed on the label.	Analytical application with tighter metal specifications	Available on request
Certified ACS	Reagent chemicals that meet or exceed the latest ACS specifications. Actual lot analysis is printed on the label.	Analytical application requiring tight specifications	Available on request
	Reagent chemicals for which the purity		

Certified	standard is established by Fisher. Purity is guaranteed to meet published maximum limits of impurities.	General analytical	Available on request
USP/NF/FCC/EP/BP	Reagent chemicals that meet or surpass specifications of the United States Pharmacopeia (USP), the National Formulary (NF), the Food Chemicals Codex (FCC), the Pharmacopeia (EP), and/or the British Pharmacopeia (BP).	Food and drug laboratories, biological testing	Available on request
Histology	Solvents and products that are specially prepared for use in the histology laboratory setting. Solvents are filtered for tissue processing applications.	Tissue processing	Available on request
Laboratory and Technical	Chemicals of reasonable purity for situations where no official standards for quality or impurity levels exist.	Manufacturing and general laboratory use	Available on request

Acronyms

- **ACS:**
  American Chemical Society. The ACS has established specifications and tests for the purity of many reagent chemicals. As the world's largest scientific society, they provide information about chemical research through publications, microfilm, satellite and computer.

- **ANSI:**
  American National Standards Institute. Administrates, coordinates, promotes and facilitates voluntary consensus standards and conformity assessment systems. Represents nearly 1,000 company, organization, government agency, institutional and international members. Does not itself develop American National Standards but facilitates development by establishing consensus among qualified groups.

- **AOAC:**
  American Organization of Analytical Chemists (now AOAC International) or Association of Official Analytical Chemists. Evolved from a group of chemists in the U.S. Department of Agriculture into an independent scientific association of analytical scientists with members located throughout the world. Provides validated methods, proficiency test samples, accreditation criteria, and scientific information to industry, government agencies, and academic institutions.

- **APHA:**
  American Public Health Association. Represents more than 50,000 members from 50+ public-health occupations. Influences policies and sets priorities affecting personal and environmental health (including federal and state funding of health programs), pollution control, chronic and infectious diseases, and professional education in public health.

- **ASTM:**
  The American Society for Testing and Materials (ASTM) is one of the largest voluntary standards development systems in the world. They have developed more than 9,000 standard test methods, specifications, classifications, definitions and recommended practices now in use. These standards encompass metals, paints, plastics, textiles, petroleum, construction, energy, the environment, consumer products, medical services and devices, computerized systems, electronics and many other areas.

- **BSI:**
  British Standards Institution. Facilitates writing the standards that industry and business use to increase efficiency and safety, and to trade internationally. Oversees implementation of management systems. Inspects commodities and tests products to ensure that they are what they claim to be and do what they claim to do efficiently and safely.

- **CAS:**
  Chemical Abstracts is branch of the ACS. Their main function is to assign a unique number—CAS (Chemical Abstracts Service Registry) number—to each chemical species.

- **EPA:**
  The Environmental Protection Agency, a branch of the U.S. government, has been entrusted with improving and preserving the quality of the environment by implementing federal laws involving clean air and water; waste site cleanup; control of insecticides, fungicides and rodenticides; toxic substances; radiation; indoor radon and ocean dumping. The EPA develops methods for lab testing of environmental pollutants and establishes specifications for some lab apparatus used in these tests.

- **FCC:**
  Published by the Food and Nutrition Board, the Food Chemicals Codex (FCC) is a compendium of specifications and test procedures for chemicals that are added directly to foods and for substances that may come into contact with foods, such as food processing aids.

- **FDA:**
  The United States Food and Drug Administration, or FDA, is the regulatory agency charged with enforcing the Federal Food, Drug and Cosmetic Act. The FDA monitors the manufacture, import, transport, storage and sale of products considered to be foods, drugs and cosmetics, as well as develops laboratory test methods for these substances and specifies types of apparatus to be used.

- **ISO:**
  The International Organization of Standardization (ISO) develops standards for quality management and quality assurance which are being adopted worldwide by businesses, to promote more uniform worldwide standards of quality and service.

- **NF:**
  The National Formulary (NF) is an official publication of the United States Pharmacopeial

Convention that presents standards and methods for analysis of pharmaceutical ingredients.

- **NFPA:**
  The National Fire Protection Association is an international nonprofit organization which produces codes and standards covering all areas of fire safety, used in nearly every country in the world. NFPA's hazard code ratings are used in laboratories to indicate the potential hazard of a chemical substance.

- **NIST:**
  The National Bureau of Standards (NBS) is now known as the National Institute of Standards and Technology (NIST), offering a full array of measurement and quality assurance services, including calibration services, standard reference materials, standard reference data and measurement assurance programs.

- **OSHA:**
  The Occupational Safety and Health Act of 1970, which requires nearly every employer to implement an industrial hygiene, safety or occupational health program, is implemented by the Occupational Safety and Health Administration (OSHA).

- **UL:**
  Underwriters Laboratories, Inc. sets standards on the construction and assembly of many types of electrical equipment, materials and appliances.

- **USDA:**
  United States Department of Agriculture. Leads Federal anti-hunger effort; is the steward of 192 million acres of national forests and rangelands and the country's largest conservation agency; brings housing, modern telecommunications, and safe drinking water to rural America; is responsible for the safety of meat, poultry, and egg products; and leads research in everything from human nutrition to new crop technologies.

- **USP:**
  The United States Pharmacopoeia, an official publication of the United States Pharmacopoeial Convention, contains standards and methods of analysis for articles used as drugs, medical devices and nutritional supplements.

Q. Is there a difference between alcohol and ethanol?

A. The term "Alcohol" can mean Pure Ethanol, Denatured Ethanol (Alcohol) or other alcohols which are not Ethanol (Ethyl Alcohol). The term "Alcohol" can refer to Pure Alcohol--undenatured Ethanol and suitable for consumption. The term "Alcohol" can also refer to pure alcohol at any level of concentration (proof). Therefore, "Pure Alcohol" is a correct term for 100% Ethanol (200 proof), 95% Ethanol (190 proof) and any concentration of Ethanol (vodka is 40% Ethanol). The term "Alcohol" can refer to Denatured Alcohol, Ethanol which is unsuitable for consumption due to the addition of toxic solvents to the pure alcohol. It

can therefore refer to any denatured ethanol product, regardless of the proof of Ethanol and the concentration of Ethanol in the denatured product. SDA-39C is referred to as Specially Denatured "Alcohol", even though it contains 1% Diethyl Phthalate as a denaturant and even though the Ethanol content of this mixture can be 190 proof or 200 proof. There are several hundred standard formulas of denatured alcohol (Ethanol), all of which can be called "Alcohol". The term "Alcohol" can refer to other solvents which are non Ethanol-based but which are chemically classified as Alcohols: Isopropyl Alcohol, Methyl Alcohol, Butyl Alcohol, and Propyl Alcohol are all "alcohol" but none are ethanol (Ethyl Alcohol). Since Fisher distributes a wide range of alcohol products, care must be taken when using the term alcohol, to communicate what product or class of products is being requested.

Q. What is the difference between pure and purity?

A. "Pure" denotes an undenatured product or a product with a single component as opposed to a mixture. "Purity" refers to the assay or percent composition of the chemical. For example, 190-Proof pure Ethanol has an assay (Purity) of 95% Ethanol and 5% water. This distinction is very important when discussing the critical levels of contaminants and other specifications of chemical products. When referring to the "purity" of a product, it is better to use the term '"assay."

Q. What is Anhydrous Alcohol?

A. "Anhydrous Alcohol" literally means no-water alcohol, but in reality it refers to low-water alcohol. This distinction is synonymous with 200-proof alcohol. Another term for anhydrous is "Punctilious". Our anhydrous grades of alcohol are always <0.3% water, and typically 0.2% water. Many are certified <0.1% water. The term "Punctilious" is used to denote a pure 200- proof alcohol. Some customers are not aware that "Punctilious" is a commercial trademark used by UCI to denote its products. It is also important to note that the term "Anhydrous" is not synonymous with the term "Pure." Pure Alcohol denotes an undenatured alcohol, which could be anhydrous or hydrated (190-proof or some other cut or proof). The term anhydrous is not unique to alcohol products. It is also used for a wide range of high purity solvents, many of which are manufactured by Fisher.

Q. What is Specially Denatured Alcohol (SDA)?

A. Specially Denatured Alcohol is pure ethanol rendered unfit for drinking by adding solvents such as methanol, ethyl acetate, or IPA in quantities specified by the Federal Government. The addition of these solvents is what "denatures" the pure alcohol, making it unfit for consumption. "Denatured" does not imply an altered ethanol molecule (as when a protein is denatured by heat or a chemical agent), but indicates that the ethanol is "spoiled" or "poisoned." Certain SDAs have additives as well as denaturants. For example, SDA-38B intended for use as a mouthwash has 1% w/v menthol as an additive. When used as a soap, it has 1% w/v lavender added. There are more than 40 SDA formulations for various applications, all of which are determined and regulated by the BATF (Bureau of Alcohol, Tobacco and Firearms).

One of the key differences between SDAs and other denatured ethanol products (General Use Formulas) is the level of added denaturants. SDAs are typically denatured at a level between 1 and 10%, and the BATF considers these products capable of being undenatured. Since there is no Federal Excise Tax collected on SDAs, the BATF wants to be sure of the intended, legal application. This is the primary reason why a permit is required for use, storage or resale of SDAs.

Specially Denatured Alcohols are used in a wide variety of common products including personal care products, flavorings,fragrances and industrial-grade products. They are also used in laboratories, hospitals and research facilities. While SDAs are not taxed, customers must obtain proper permits from the BATF in

order to use more than 5 gallons of denatured product in a one-year period. Products which do not require a BATF permit are referred to as "General Use Formulas". Fisher has the capability of manufacturing all SDAs but chooses not to produce certain formulas due to the carcinogenic nature of certain denaturants the extreme danger hazardous denaturants may pose.

Q. What is Completely Denatured Alcohol?

A. Completely Denatured Alcohol has a minimum level of denaturant (approximately 5%). Although the amount of denaturant is minimal, CDA does not require a permit by the BATF due to the type of denaturant used, which is considered to be very offensive (i.e., MIBK with gasoline or kerosene). However, the manufacture, resale, transport, storage and use of CDA are subject to certain Federal regulations and documentation. Completely Denatured Alcohol may not be used in manufacturing products for internal human use or consumption if any of the alcohol or its denaturants remain in the finished product.

Q. What is the difference between natural and synthetic?

A. Ethanol products can be made with naturally derived ethanol (commonly referred to as "grain" alcohol), or synthetically produced ethanol. Natural alcohol is commonly referred to as grain alcohol because almost all of the commercial alcohol produced in North America is derived from grain (corn). However, ethanol can also be produced naturally (fermented) from any carbohydrate source, such as wheat, cane, beet and fruits like grape and apple. While grain and synthetic alcohols are technically the same (the molecule is identical), there are differences in the amounts of contaminants (sec-butanol, acetone and methanol) in each. . An experienced chemist with a High Resolution Gas Chromatograph can detect the difference in grain and synthetic by looking at these contaminants in the parts-per-million (ppm) range.

Q. What is the difference between 190-proof and 200-proof?

A. All ethanol products--whether pure or denatured, natural or synthetic--have a proof, which is a measure of water content. Any level of proof can be produced based on the amount of water added (referred to as dilution or cut of water).

Proof can also be derived by calculating two times the actual ethanol concentration by volume. Industrially, the majority of ethanol products, whether pure or denatured, can be classified as 200-proof or 190-proof. The third most common proof is 192, used primarily in beverage-grade applications. Proof, then, is a measure of the water or ethanol content of pure or denatured alcohol, even if the ethanol is only one component of the finished product. all ethanol products should be referred to and requested by proof.

Q. What is the difference between Taxable and Nontaxable Alcohol?

A. Pure alcohol is considered taxable alcohol. The federal government requires an excise tax of $13.50 per proof gallon (200-proof pure alcohol = $27.00/wine gallon). A tax-exempt certificate is required to be on file with Fisher for us not to charge the federal excise tax on pure alcohol. The excise tax is paid immediately to the Federal government. Fisher does not make any profit from collecting or handling the excise tax, nor does it receive aportion of it as a fee. All other denatured ethanol products do not require the payment of a Federal Excise Tax. Only customers with an exemption from paying the Federal Excise Tax on Alcohol are free from paying this tax. Eligibility for exemption is determined by the BATF and not Fisher.

Q. Is there a difference between "Proof Gallon" and "Wine Gallon?"

A. Yes. The federal government taxes by the "Proof Gallon", so the proof becomes significant in taxable situations. For instance, 200-proof pure ethanol has two "Proof Gallons" per every one gallon of alcohol. The actual physical quantity of one gallon is then referred to as a "wine gallon." 190-proof ethanol has 1.9 proof gallons per wine gallon of ethanol.

Q. Can pure ethanol be purchased without a BATF permit?

A. Yes, but a federal excise tax must be paid. Current federal tax is $13.50 per "Proof Gallon," which is $27.00 per gallon for 200-proof ethanol. Fisher includes the federal excise tax in your invoice.

Q. Can specially denatured alcohol be bought without a BATF permit?

A. Yes, but purchases are limited to up to 5 gallons of SDA product in one year A BATF permit is required to purchase more than 5 gallons in one year.

Q. I need custom packaging. Can you do this?

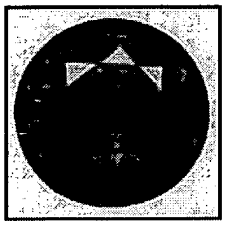
A. Yes. Fisher custom-packages many chemicals. Contact your Fisher representative for details.

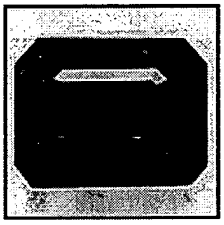
Q. I need chemicals that comply with international testing requirements. Can Fisher supply these items to me?

A. Yes. Fisher's certifies many products to various international specifications. Please contact your Fisher representative with your request.

Gemstone Library

Natural Ruby





RUBY is the red variety in the corundum family and has been one of the world's most valued gemstone for many centuries.

Origin	Burma, Vietnam, Cambodia, Thailand, Africa, Madagascar.
Color	red, orangey red, pinkish red, violetish red
Refractive Index	1.759-1.778
Chemical Composition	AL_2O_3
Hardness	9
Density	4
Crystal Structure	Hexagonal
Zodiac Sign	Leo
Planet	Sun
Month	January
Anniversary	15th and 40th

Fine Rubies, especially Burmese rubies are among the rarest and most expensive gemstones in the world. Prized for their beauty, durability, and rarity, it is the quality of the color which most determines the value of the stones. The ideal color is that of a red traffic light, a highly fluorescent red of high intensity. Demand for gem quality Ruby has always been strong with mining records from Burma dating back almost 500 years.

The word ruby comes from the Latin word for red -- ruber. They are a form of corundum which is colorless in its pure state. The red color is produced by small traces of chromium. Traces of iron make the color more brown. Although Burmese, African, Thai and Cambodian rubies have the same chemical and physical properties, they differ noticeably in color and hue.

Burmese rubies are the best rubies in the world and the most sought after. Burma ruby is the rubies that we specialize in. Burma ruby displays a true red to pinkish red color in most kinds of light.

African, Thai and Cambodian rubies are usually much darker and browner in color and similar to garnet. Many rubies on the market have been heated to enhance the color. This is a generally accepted practice in the gem trade and gem labs classify them as natural rubies.

Rubies and Sapphires which are both members of the corundum family have the same hexagonal crystallographic structure. The basic chemical formula is AL2O3; is the same for both ruby and sapphire. It is the presence of trace elements like chromium, iron, vanadium and titanium which are responsible for the wide range of colors in which the mineral occurs. The red color in Rubies is primarily a result of the presence of chromium. Red corundum is known as Ruby and any other color is called a sapphire. In practice however, the determination is not always so straight forward because there are no internationally accepted standards for the color of a ruby. Gemologists could describe the same stone as a pinkish red ruby or a pinkish red sapphire and borderline cases are not uncommon.

The heating of Rubies and Sapphires is quite common and an accepted enhancement process (when no other color enhancing elements are added) which can improve the transparency and the color of the stones in a natural way. Techniques range from simply throwing gems into a fire to be cooked to employing sophisticated electric or gas furnaces at specific pressures and atmospheric conditions. The treatment is permanent and heated stones do not require special care. We at AJS Gems, wash and re-cut all our rubies so they have no surface pits filled with any glass-like material (glass fill). We sell only Natural Gemstones.

Gem quality rubies are rare and rarely large, clean stones are always a rarity. The most notable deposits of Ruby occur in Burma, Vietnam, Thailand, Cambodia, Tanzania, Kenya, and Madagascar. Ruby is also found in Colombia, Afghanistan, Pakistan, India and in the U.S.A.

Vietnam: abounds in natural resources and precious gemstones in particular. Vietnam's two largest Ruby mines are Yen Bai and Nghe An. Vietnam gemstones such as Ruby, Star Ruby, sapphire, spinel and zircon have been inconsistent in recent years. Vietnam's Ruby is highly valued in terms of quality, with the best said to be equal to that of Burma.

Madagascar: The most recent discoveries of Rubies have occurred in Madagascar at Andilamena and Vatomandry. The deposits differ significantly with respect to their mineralogical and gemological properties. The deposit in Vatomandry produces crystals of nice natural orange/red and pinkish color which do not require heating.
The deposit in Andilamena is more substantial and seems have been the focus of most of the recent production.
Like many parts of Madagascar, there are gems but no roads to get to them most people just walk.
The deposit is of a primary character and probably igneous in origin.
The rough is generally somewhat violet and not very clean. Heat treatment can dramatically improve the color and many of the resulting stones will show a color similar to that of rubies from Thailand, red with a brown secondary tone.

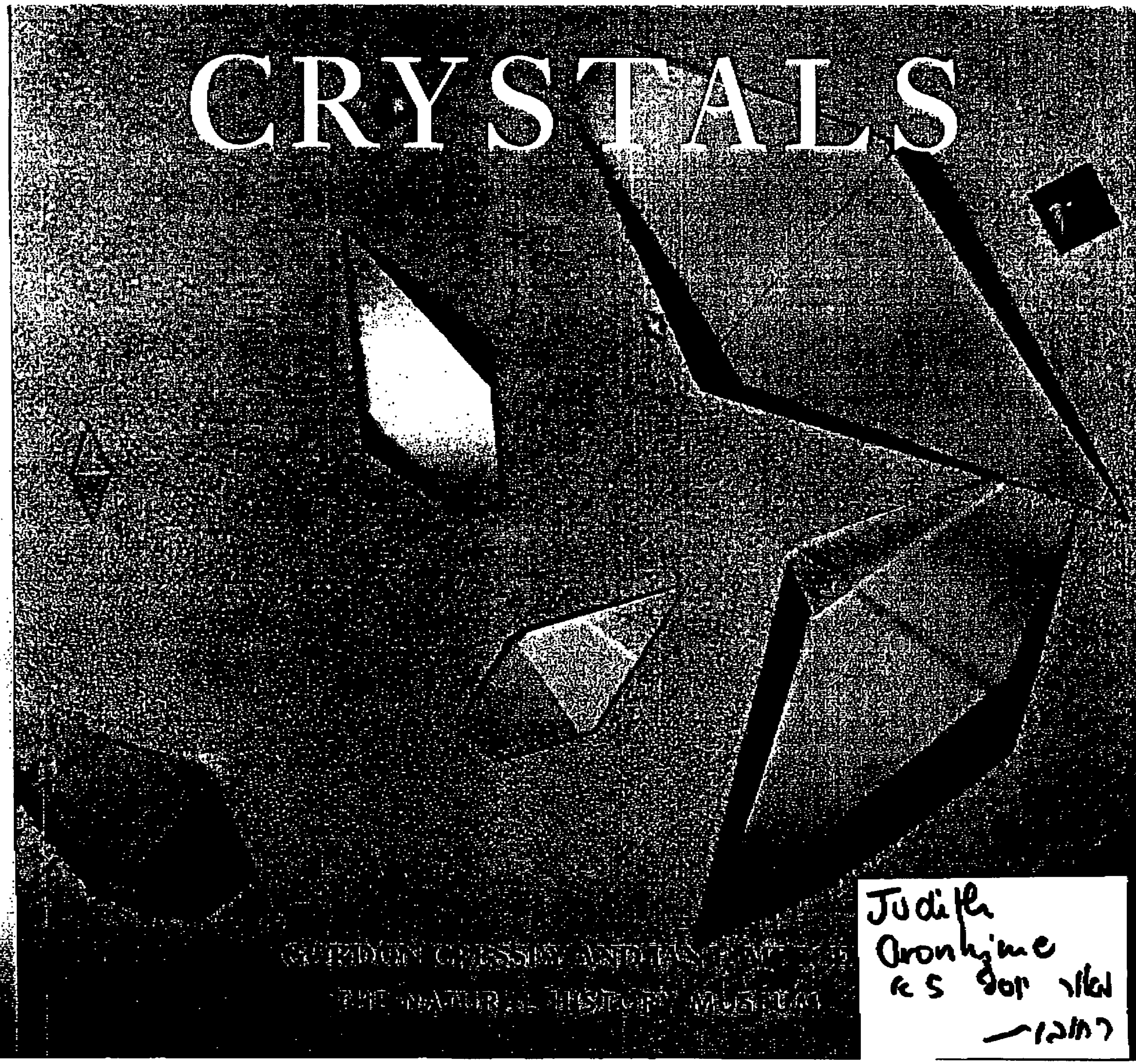
Tanzania: Tanzanian Rubies from the Songea deposit are darker and more garnet like in color than Burmese Rubies. Their garnet like appearance can be misleading and even jewelers can be confused. The color of most gems tends to lighten as the size is reduced and the color of Songea Rubies is frequently best in the smaller sizes.

Burma: Burmese Rubies are considered the best, for one simple reason there color. The most famous localities for Rubies are in the districts around Mogok in northern Burma and at Mong Hsu about 250km east of Mandalay. Burmese Rubies are known for their fine fluorescent red

color in any kind of light. The color of Burmese stones is often said to be "pigeons blood". Many of the Rubies are bright red and may contain traces of blue or pink. Rubies are rarely clean and the prices for Burma Rubies are higher than that of Rubies from any other deposits.

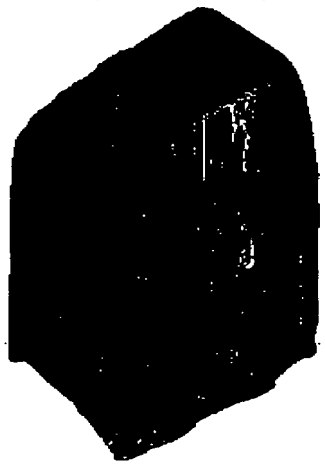
Ruby has been the world's most valued gemstone for thousands of years. It was said to be the most precious of the twelve stones God created when he created all things and this "lord of gems" was placed on Aaron's neck by God's command. Ruby brings you serenity, and protect you against injury.

Color
Gemstone Cut
Gemstone Shape
Gemstone Glossary
Proper Care of Gemstones
Hardness
Refractive Index
Crystal Structure
Density
Chemical Composition
Gemstone Weight Chart
Metric to Inch Conversion Chart
Diamond Weight Chart
Gemstones & Zodiac
Recommended Gem Books
Ruby
Sapphire
Tourmaline
Other Gemstones


CRYSTALS
GORDON CRESSEY AND IAN F. MERCER
THE NATURAL HISTORY MUSEUM
Judith Aronhime

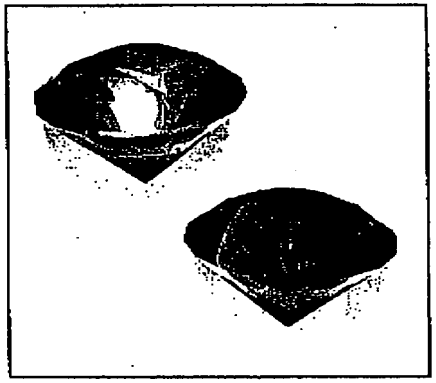
GEM QUALITY CRYSTALS

Certain minerals and some man-made crystals are cut and polished into gemstones. To qualify as such, they should be hard and tough, be 'crystal' clear and have a beautiful colour. Rarity or special physical properties will enhance the value of gemstones, as will fashion. The majority of gemstones are silicates (e.g. emerald and amethyst). Ruby and sapphire are both composed of aluminium oxide (corundum) with different kinds of impurity atoms. Diamond is composed of a single element – carbon, and is the hardest substance known. A skilled lapidary can turn a rough-shaped crystal into a sparkling gem by carefully cutting and polishing facets around the stone at angles designed to reflect the maximum amount of light entering the gem (figs 34, 38). The interaction of light with a gem (its optical properties, see page 26) provides a means of identifying the crystalline substance from which the gem was cut (figs 35, 36).



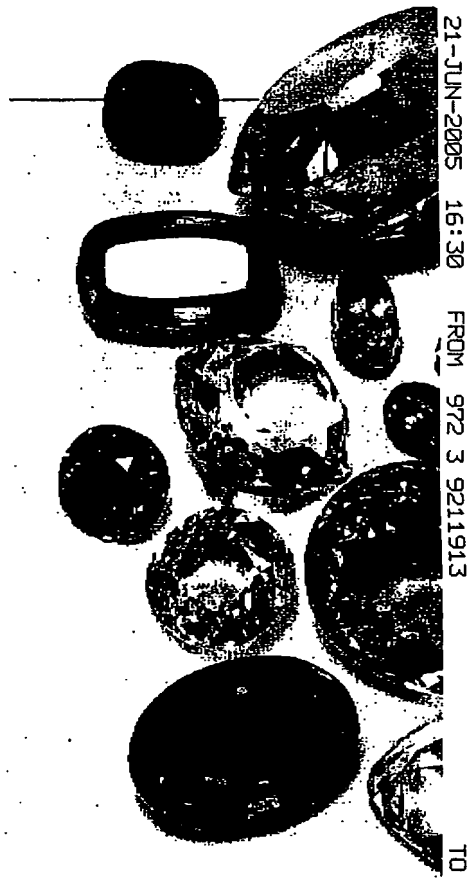
34 A faceted tanzanite cut from a gem quality crystal.

35 Double refraction of light by sinhalite gem.



36 Varied colour effect as an iolite gem is turned.

37 Jade: tough rock of interlocked crystals.



38 Gem quality crystals, faceted to reveal their clar

Crystal chemistry of gems

Many silicate and oxide minerals are hard transparent and resistant to wear and corrosion. These qualities make them suitable for use as gemstones. However, the colour of the mineral often determine whether it will be used as a gemstone. For example, the mineral beryl – a beryllium aluminium silicate – is colourless, but a tiny amount of chromium in its structure (in place of some of the aluminium atoms

GEM QUALITY CRYSTALS

38 Gem quality crystals, faceted to reveal their clarity, colour and beauty.

uble refraction of light by sinhalite gem.

aried colour effect as an iolite gem is turned.

de: tough rock of interlocked crystals.

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WO 02/102382 A1

(54) Title: A PROCESS FOR PREPARING PAROXETINE HCl WHICH LIMITS FORMATION OF PINK COLORED COMPOUNDS

(57) Abstract: The present invention provides a process for preparing paroxetine HCl from paroxetine base which provides paroxetine HCl substantially free of pink-colored compounds or an impurity identified by an HPLC RRT of about 1.5. The processes of the present invention utilize a buffer, a molar ratio of HCl to paroxetine base of less than one, and crystallize/recrystallize in the presence of an effective amount of an anti-oxidant. A preferred way to create a buffer is by using ammonium chloride. A preferred anti-oxidant is ascorbic acid. The present invention also provides for re-crystallizing paroxetine HCl prepared by the above methods or any other methods in the presence of an effective amount of an anti-oxidant such as ascorbic acid. A preferred solvent system for recrystallization is a mixture of acetone and methanol. Processes of the present invention can combine these various features.

A PROCESS FOR PREPARING PAROXETINE HCl WHICH LIMITS FORMATION OF PINK COLORED COMPOUNDS

CROSS-REFERENCE TO RELATED APPLICATIONS

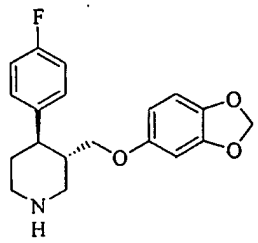
This application claims priority to provisional applications Serial No. 60/298,603, filed June 14, 2001; Serial No. 60/326,993, filed October 5, 2001 and Serial No. 60/346,048, filed January 4, 2002, the contents of which are incorporated herein by reference.

FIELD OF THE INVENTION

The present invention relates to paroxetine, more particularly, a process for the preparation of paroxetine HCl.

BACKGROUND OF THE INVENTION

Paroxetine, (-)-*trans*-3-[(1,3-benzodioxol-5-yloxy)methyl]-4-(4-fluorophenyl) piperidine; (3S, 4R)-3-[5-(1,3-dioxaindanyl)oxymethyl]-4-(p-fluorophenyl)piperidine, is a 5-hydroxytryptamine (5-HT, serotonin) re-uptake inhibitor having the formula:



Paroxetine

Paroxetine, disclosed in U.S. Pat. No. 4,007,196, is prescribed for the treatment of, *inter alia*, depression, Parkinson's disease, anxiety disorders, obsessive-compulsive disorders, panic disorder and post-traumatic stress disorder. Other syndromes such as pre-menstrual syndrome (PMS) can also be treated with paroxetine. Paroxetine is marketed as Paxil® in dosage forms containing about 10-40 mg of paroxetine HCl.

A problem with paroxetine HCl tablets is that they often undergo a color change

over time. For example, U.S. Pat. No. 6,113,944, discloses that tablets of paroxetine HCl often develop an undesirable pink hue. The '944 patent discloses that formulations of paroxetine HCl prepared in an anhydrous environment have a less likelihood of developing a pink hue.

Without being bound by theory, it is believed that impurities in paroxetine hydrochloride play a role in the color change to pink. The level of the impurities in paroxetine that are associated with a color change to pink can be analyzed in two different manners. One approach is a simple visual analysis, *i.e.*, observing if a sample of paroxetine HCl has turned pink. Another approach is to measure the degree of an impurity identified by a high pressure liquid chromatography ("HPLC") relative retention time ("RRT") of about 1.5. The different UV-spectrum characteristic of this impurity has linked the impurity to the development of a pink color. A color change however can occur even if this impurity is present at low levels, suggesting that other impurities may also play a role in the color change. Purification steps to remove this impurity such as by crystallization, extraction, chromatography or other separation procedures are often ineffective.

Thus, there exists a need in the art to prepare paroxetine HCl and its formulations that do not undergo a color change, particularly to pink, during storage.

SUMMARY OF THE INVENTION

In one aspect, the present invention is directed to a process for preparing paroxetine HCl comprising reacting paroxetine base with less than one base equivalent of HCl, and separating the paroxetine HCl. The molar ratio of HCl to paroxetine base used is preferably from about 0.75 to about 0.95, more preferably from about 0.80 to about 0.90, and most preferably about 0.85

In another aspect, the present invention is directed to a process for preparing paroxetine HCl comprising converting paroxetine base to paroxetine HCl at a pH of greater than about 3.0, and separating the paroxetine HCl. Preferably, the pH is from about 3 to about 8.

In another aspect, the present invention is directed to a process for preparing paroxetine HCl comprising contacting paroxetine base with HCl in a buffer, and separating the paroxetine HCl. Preferably, a weak acidic reagent such as ammonium chloride is

added to create a buffer while HCl is added to complete the reaction.

In another aspect, the present invention is directed to a process for preparing paroxetine HCl comprising converting paroxetine base to paroxetine HCl and separating the paroxetine HCl, wherein at least a portion of the process occurrs in the presence of an effective amount of an anti-oxidant and optionally active carbon. A preferred anti-oxidant is ascorbic acid. A preferred amount of ascorbic acid used is from about 0.05 to about 10%, more preferably from about 0.10 to about 10% ascorbic acid (wt/wt% of ascorbic acid to paroxetine base). Preferably, the anti-oxidant is used in combination with active carbon.

In another aspect, the present invention is directed to a process for preparing paroxetine HCl comprising recrystallizing paroxetine HCl in the presence of an effective amount of an anti-oxidant and optionally active carbon, and separating the paroxetine HCl.

The various aspects of the present invention can be combined into a single process. For example, paroxetine base can be contacted with less than one base equivalent of HCl in the presence of a buffer, followed by crystallization in the presence of an anti-oxidant, and optionally active carbon. Alternatively, paroxetine HCl prepared by contacting paroxetine base with less than one base equivalent of HCl and an effective amount of anti-oxidant, can be re-crystallized in the presence of an effective amount of anti-oxidant.

A particularly preferred solvent for the processes of the present invention is toluene, and mixtures of toluene and PGME. A preferred solvent system for re-crystallization of crude paroxetine HCl is a mixture of acetone and methanol.

The present invention is also directed to paroxetine HCl prepared by the processes of and, pharmaceutical compositions thereof containing a pharmaceutically effective amount of paroxetine HCl and a pharmaceutically acceptable excipient, methods of administration thereof.

FIGURES

Figure 1 is the HPLC chromatogram for example 2.

Figure 2 is the HPLC chromatogram for example 3.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to novel processes for preparing paroxetine HCl which limit or prevent the formation of pink-colored compounds and/or the amount of an impurity identified by an HPLC RRT of about 1.5 by manipulating the equivalent ratio of HCl, using a buffer, using an anti-oxidant, or a combination thereof. The processes of the present invention limit the formation of impurities believed to be associated with a undesirable color change to pink, including an impurity identified by an HPLC RRT of about 1.5.

As used herein, "pink" has its ordinary meaning and refers to any of a group of colors reddish in hue, of medium to high lightness, and of low to moderate saturation. The term "rose" instead of "pink" is used synonymously in applications to which this application claims priority.

Paroxetine HCl is generally prepared by contacting paroxetine base with a slight excess of concentrated HCl. Such method for conversion however has drawbacks. The use of excess HCl without a buffer can lead to a rapid drop of pH to a pH of about 1 or less. Paroxetine has an acetal group (methylenedioxy), which can hydrolyze relatively easily under such strongly acidic conditions. Additionally, the use of an excess molar ratio of HCl can lead to deterioration of the final product. It is believed that the presence of excess HCl can accelerate acetal hydrolysis by becoming trapped in the final product.

The present invention provides processes designed to address the above drawbacks, thereby limiting the formation of impurities associated with an undesirable change of color to pink.

In one embodiment of the present invention, paroxetine HCl is prepared by contacting paroxetine base with HCl in a buffer. In this embodiment, a weak acid sets up a buffer while HCl is added at an equivalent of less than 1 to complete the conversion to the HCl salt. Preferably, the pH of the reaction mixture is greater than about 3, more preferably from about 3 to about 8.

As used herein, a "weak acid" refers to an acid that does not substantially completely ionize in water. A weak acid has a positive pKa. Ammonium ions, for example, which form as a result of dissociation of ammonium chloride in water, have a pKa of 9.24. An aqueous system employing a weak acid will typically have a pH of above about 3.

The reaction can be carried out by preparing a buffered aqueous solution, and a

solution of the base in an organic solvent. The two solutions are then mixed together. Depending on the miscibility of the organic solvent with the aqueous phase, a one or a two phase system is created. Preferably, a one phase system is obtained by using an organic solvent such as toluene that is miscible with the aqueous solution. The mixture of such organic solvents can also be used.

The aqueous solution is buffered by a weak acid. Ammonium chloride is a preferred weak acidic reagent. One of skill in the art can appreciate that ammonium chloride is a salt and its dissolution in an aqueous medium creates ammonium ions, which are the weakly acidic species.

When using a weak acidic reagent such as ammonium chloride, HCl is used to finish the reaction. Particularly when using ammonium chloride, ammonia builds up as the reaction proceeds, resulting in an increase in pH. The addition of HCl maintains a desired pH range.

The organic phase containing paroxetine base can be prepared by dissolving paroxetine base in an organic solvent, or a mixture of such solvents. Examples of such solvents include toluene and glycol monoethers. The use of toluene as a solvent is preferred due to a substantial difference in the solubility of paroxetine base and paroxetine HCl in toluene. Paroxetine base is substantially soluble in toluene, while paroxetine HCl is usually soluble in toluene only at high temperatures, such as reflux. The difference in solubility allows for the crystallization of the HCl salt upon formation thereof, facilitating the separation of the salt and further driving the equilibrium towards salt formation. Other preferred solvents include alcohols such as isopropanol.

Preferably, a mixture of toluene and glycol monoethers is used. The mixture used is preferably from about 8:1 to about 4:1 toluene to glycol monoethers, with a ratio of about 6:1 being preferred. The term "glycol monoethers" refers to the mono-(C_1-C_6, straight- or branched-chain)alkyl ethers of lower alkylene glycols such as, for example, ethylene glycol, propylene glycol, 1,3-butylene glycol and 2,3-butylene glycol. Among preferred glycol monoethers are, for example, ethylene glycol monomethyl ether ("methyl cellosolve", 2-methoxyethanol), ethylene glycol monoethyl ether ("ethyl cellosolve", 2-ethoxyethanol) and propylene glycol monomethyl ether ("PGME", 1-methoxy-2-propanol). Use of PGME is preferred.

After mixing of the two solutions, the base converts to the HCl salt and crystallizes

out of the mixture. The resulting mixture can be cooled to accelerate the crystallization of the HCl salt, preferably to a temperature of from about 0°C to about 10°C, more preferably to below about 5°C. The mixture can also be stirred, both to accelerate conversion to the HCl salt and to induce crystal formation.

The resulting crystals can then be separated by techniques well known in the art, such as filtration. After separation, the crystals can be washed, with an aqueous solvent such as water and a non-aqueous solvent such as toluene and then dried. The product can be dried from a temperature of from about 50°C to about 80°C. The pressure can be reduced to accelerate the drying process.

In another embodiment, paroxetine base is contacted with less than one base equivalent of HCl in the absence of a buffer. A solution of paroxetine base in an organic solvent or a mixture of solvents such as toluene and monoethers of glycol is prepared as described above. HCl is then added to the solution in a molar ratio of less than one to form paroxetine HCl. Preferably, the molar ratio of HCl to paroxetine base used is from about 0.75 to about 0.95 base equivalent, more preferably from about 0.80 to about 0.90, and most preferably about 0.85.

The solution can be cooled to accelerate the crystallization of the HCl salt, preferably to a temperature of from about 0°C to about 10°C, more preferably to below about 5°C. The resulting mixture can be stirred, both to accelerate conversion to the HCl salt and to induce crystal formation. If an aqueous medium is used, the pH of the reaction is preferably above about 3, more preferably from about 3 to about 8.

The resulting crystals can then be separated by techniques well known in the art, such as filtration. After separation, the crystals can be washed, with an aqueous solvent such as water and a non-aqueous solvent such as toluene and then dried. The product can be dried from a temperature of from about 50°C to about 80°C. The pressure can be reduced to accelerate the drying process.

In another embodiment, the HCl salt is prepared by carrying out at least a portion of the preparation of paroxetine HCl in the presence of an anti-oxidant. As used herein, an anti-oxidant has its ordinary meaning in the art and refers to a compound or a chemical substance that inhibits oxidation. One of skill in the art would appreciate that different anti-oxidants known in the art can be used with the present invention. The anti-oxidants used are preferably small organic molecules. Examples of such anti-oxidants include

ascorbic acid (Vitamin C), butylated hydroxytoluene (BHT), butylated hydroxyalanine (BHA), with ascorbic acid being preferred. An effective amount of ascorbic acid, preferably from about 0.05 to about 10%, more preferably from about 0.10 to about 10 % ascorbic acid (wt/wt% of ascorbic acid to paroxetine base) is used to provide paroxetine HCl product in accordance with the present invention. As one of skill in the art can appreciate, the preferred ratio of other anti-oxidants to paroxetine base can be determined in a routine fashion, with the preferred ratio for ascorbic acid being used as a guidance in such instance.

To crystallize the paroxetine HCl salt, HCl can be added to a solution of paroxetine base and an anti-oxidant in a suitable solvent. In a particularly preferred embodiment, HCl is added at a molar ratio of less than one base equivalent. Preferably, the molar ratio of HCl to paroxetine base used is from about 0.75 to about 0.95 base equivalent, more preferably from about 0.80 to about 0.90, and most preferably about 0.85.

A preferred solvent for the reaction is toluene. Other suitable solvents include alcohols. Preferably, in addition to an anti-oxidant, active carbon is added to the reaction mixture, which further improves decoloration. The amount of active carbon used is preferably from about 0.5 to about 1 gram of active carbon per about 100 ml of solution.

The reaction mixture can be stirred, and the temperature reduced to from about 0°C to about 10°C, more preferably to below about 5°C, to accelerate crystallization. The formed crystals can then be separated by techniques well known in the art, such as filtration. After separation, the crystals can be washed with toluene and water, and dried to give paroxetine HCl. The product can be dried from a temperature of about 50°C to about 80°C. The pressure can be reduced to accelerate the drying process. The paroxetine HCl so prepared can optionally be re-crystallyzed in the presence of an effective amount of an anti-oxidant and/or active carbon.

The anti-oxidant can be added at various times during preparation of paroxetine HCl. For example, the anti-oxidant can be present upon contacting paroxetine base with HCl or added after the conversion of the paroxetine base to paroxetine HCl. The presence of the anti-oxidant at least during crystallization of paroxetine HCl is preferred. Preferably, the anti-oxidant is introduced after the conversion to paroxetine HCl, but before crystallization of the HCl salt. In either case, the final product, *i.e.*, paroxetine HCl in solid form, is substantially free of anti-oxidants.

Crytallization in the presence of an anti-oxidant can be used in conjunction with the embodiments in which paroxetine HCl is prepared by using an HCl equivalent of less than one or the embodiment using a buffer, as described herein above. For example, paroxetine base and an effective amount of an anti-oxidant can be dissolved in an organic solvent such as toluene. The resulting solution can then be added to an aqueous solution containing a weak acid. HCl can then be added as described above in a ratio of less than about one base equivalent.

Paroxetine HCl can also be re-crystallized in the presence of an effective amount of an anti-oxidant such as ascorbic acid. To carry out the re-crystallization, paroxetine HCl is dissolved in a suitable organic solvent such as toluene. The toluene is preferably heated to reflux to increase its solubility for paroxetine HCl. Ascorbic acid, preferably with active carbon, is then added to the solution. If active carbon is added, it is subsequently removed, preferably by filtration.

After filtration, the filtrate can be cooled to a temperature of from about 0°C to about 10°C, with less than about 5°C being preferred, to accelerate the crystallization process. The crystals are then separated by techniques well known in the art, such as filtration. The crystals can then be washed with an organic solvent such as toluene and a non-organic solvent such as water.

The crude paroxetine HCl prepared by the embodiments of the present invention is preferably recrystallized in an acetone/methanol solvent system, optionally in the presence of an anti-oxidant. Paroxetine HCl is added to a mixture of acetone and methanol, preferably from about a 10:1 to about 30:1, more preferably about a 20:1 mixture. Preferably, an effective amount of ascorbic acid is also added to the mixture. The mixture can be heated, preferably to reflux, to form a solution. The solution is then passed through a charcoal bed to remove impurities. The filtrate is then cooled, preferably to slightly above 0°C, and a precipitate forms. The precipitate, paroxetine hydrochloride hemihydrate, is then separated by techniques well known in the art such as filtration and preferably dried. Two preferred schemes of the present invention are disclosed in Table-1.

Table-1--The schemes illustrated are similar, except scheme II does not use a buffer.

Preferred Scheme I	Preferred Scheme II
<1 molar equivalent of HCl	Same
ammonium chloride as a buffer	None

Crystallization in the presence of an effective amount of ascorbic acid	Same
Re-crystallization in the presence of an effective amount of ascorbic acid using a 20:1 mixture of acetone and methanol.	Same

The paroxetine hydrochloride of the present process is substantially free of impurities associated with a color change to pink, and is less susceptible, if at all, to develop a pink color overtime These impurities include the impurity identified by an HPLC RRT of about 1.5. Retention time refers to the time required for a compound to pass from the point of injection to the detector. Preferably, the processes of the present invention result in a final product having less than about 0.1% (HPLC area percentage) of the impurity identified by an HPLC RRT of about 1.5. After storage for at least four days at room temperature and a relative humidity of about 60-80%, the level of the impurity identified by an HPLC RRT of about 1.5 is preferably less than about 0.22, more preferably less than about 0.12 and most preferably less than about 0.02 (HPLC area percentage). HPLC area percentage refers to the sum of all the areas under the peak of an impurity in a chromatogram divided by the sum of all the areas under the peaks of all of the other compounds represented in the chromatogram.

The paroxetine hydrochloride of the present invention, in addition to analysis of the amount of the impurity identified by an HPLC RRT of about 1.5, can be analyzed visually for a color change. Preferably, the paroxetine HCl of the present invention remains substantially color-free upon long-term storage. In particular, the paroxetine HCl does not develop a pink color. The paroxetine HCl made in accordance with the present invention can be used to make storage-stable compositions which do not, or are substantially less susceptible, to becoming pink-colored during storage.

One visual analysis can be carried out by preparing a solution of about 2 mg/ml of paroxetine HCl prepared in a mixture of about 0.05M di-Potassium hydrogen phosphate buffer and about 35% of acetonitrile. If the product is substantially free of the impurities associated with a pink color, the solution does not develop a pink color after sitting for about 20 minutes. Preferably, the solution of the paroxetine HCl of the present invention is color free for at least about 20 minutes. On the other hand, available commercial products usually produce a pink colored solution under similar conditions.

Another visual analysis can be carried out by observing the color of paroxetine hydrochloride during storage. Preferably, the paroxetine HCl of the present invention is substantially free compounds associated with a pink color for at least four days at a temperature of about 55°C and a relative humidity of about 60-80%. One of skill in the art can appreciate that the level of the compounds associated with a pink color can vary according to the temperature and other conditions used for storage.

One of skill in the art can appreciate that the processes of the present invention can be used to prepare different forms of the HCl salt. The HCl salt of paroxetine exists in at least two solid state pseudopolymorph forms differentiated by their degree of hydration. Form I is a non hygroscopic hemihydrate and is thermodynamically more stable. Form II is a hygroscopic anhydrate. Form II converts to Form I if seed crystals of Form I are present, when exposed to humid conditions, or if subject to compression. Commercial paroxetine tablets such as Paxil® usually contain paroxetine HCl hemihydrate.

Paroxetine HCl also exists in other polymorphic forms and solvates of various different solvents. A particularly preferred solvate is the isopropanolate.

The processes of the prior art can be modified according to the teachings of the present invention to prepare the various forms of paroxetine HCl. Crude paroxetine HCl hemihydrate can be formed, for example, from a toluenic solution of paroxetine base by contacting the solution of paroxetine base with aqueous HCl followed by crystallization in an appropriate solvent as generally disclosed in U.S. Patent No. 4,721,723. Crystalline paroxetine HCl hemihydrate can then be prepared by recrystallization of the crude paroxetine HCl hemihydrate in a suitable solvent. Among suitable solvents are included, for example, lower alkanols such as methanol and ethanol; ketones such as acetone; esters such as ethyl acetate; and, mixtures of any of the foregoing such as methanol/acetone.

The prior art discloses various processes for preparing anhydrous forms of paroxetine HCl, as generally disclosed for example in U.S. Patent No. 6,080,759. The prior art discloses preparing anhydrous paroxetine HCl by contacting, in a dry N_2 environment, a solution of paroxetine base in an organic solvent, such as isopropanol, with dry HCl gas. Alternatively, the solution of paroxetine base in an organic solvent can be contacted with a solvent substantially free of water wherein the solvent has dry HCl gas dissolved therein. These prior art processes can be modified for crystallization in the presence of ascorbic acid or the use of a certain molar ratio of HCl.

Paroxetine hydrochloride anhydrate can be prepared via the hemihydrate or other solvates. As disclosed in U.S. Patent No. 6,080,759, anhydrate forms of paroxetine free of bound solvent can also be prepared from the paroxetine hemihydrate by dissolving the hemihydrate in an appropriate solvent substantially free of water which forms an azeotrope with water. Suitably, solvent is removed by distillation and fresh solvent is added until all of the water is removed.

Paroxetine HCl anhydrate can also be made by crystallizing paroxetine HCl in an organic solvent or a mixture of solvents which form a solvate with the paroxetine HCl and displacing the solvated solvent or solvents from the paroxetine HCl solvate using a displacing agent. Preferably, gaseous or liquid water can be used as the displacing agent. It is important that the paroxetine HCl solvate is contacted with enough water and for sufficient time to displace the solvent but insufficient to cause conversion to the HCl hemihydrate.

Paroxetine HCl can also be prepared in various solvate forms as disclosed in U.S. Pat. No. 6,080,759, the processes of which can be modified according to the teachings of the present invention. Among the preferred solvate forms is paroxetine HCl isopropanolate as disclosed for example in Examples 1-3 of U.S. Patent No. 6,080,759. Paroxetine HCl isopropanolate can be formed by displacing water from paroxetine HCl hemihydrate in, e.g., a mixture of toluene and isopropanol followed by crystallization. Paroxetine HCl isopropanolate can also be formed by contacting a solution of paroxetine base in isopropanol with dry HCl gas followed by crystallization. The isopropanolate can also be formed by contacting a solution of paroxetine base in dry isopropanol with a solution of dry HCl gas in dry isopropanol followed by crystallization. Solvates other than the isopropanolate can be made by similar methods as disclosed in U.S. Patent No. 6,080,759. Among such solvates are included solvates from solvents such as alcohols other than isopropanol such as 1-propanol and ethanol; from organic acids such as acetic acid; from organic bases such as pyridine; from nitriles such as acetonitrile; from ketones such as acetone and butanone; from ethers such as tetrahydrofuran; from chlorinated hydrocarbons such as chloroform and from hydrocarbons such as toluene. These solvates can be used to form the anhydrate forms free of bound solvent by either displacing the solvent as described above or by removing the solvent by conventional techniques such as vacuum oven drying.

The term paroxetein HCl as used in the present invention includes all these and other polymorphs, solvates and forms of paroxetine hydrochloride.

In accordance with the present invention, the highly pure forms of paroxetine HCl prepared by the new methods disclosed herein can be prepared as pharmaceutical compositions that are particularly useful for inhibiting the re-uptake of serotonin. Such compositions can include any of the various forms of the HCl salt in combination with pharmaceutically acceptable carriers and/or excipients known to one of skill in the art.

For example, these compositions may be prepared as medicaments to be administered orally, parenterally, rectally, transdermally, bucally, or nasally. Suitable forms for oral administration include tablets, compressed or coated pills, dragees, sachets, hard or gelatin capsules, sub-lingual tablets, syrups and suspensions. Suitable forms of parenteral administration include an aqueous or non-aqueous solution or emulsion, while for rectal administration suitable forms for administration include suppositories with a hydrophilic or a hydrophobic vehicle. For topical administration, suitable transdermal delivery systems known in the art, and for nasal delivery, suitable aerosol delivery systems known in the art, may be employed.

A particularly preferred unit dosage form is a coated tablet. Such tablet contains a pharmaceutically effective amount of the paroxetine HCl of the present invention in conjunction with one or more excipients, such as a binder, filler, stabilizer, disintegrant, glidant, flavoring and coloring agents. An effective amount of paroxetine HCl is approximately from about 10 mg to about 200 mg of the base equivalent of paroxetine HCl, as disclosed in U.S. Pat. No. 6,080,759, more preferably from about 10mg to about 100mg, and most preferably from about 10 to about 50 mg.

Suspensions, containing a dosage of about 10 mg of the base equivalent of paroxetine HCl per 5ml of liquid are also included within the scope of the pharmaceutical compositions of the present invention. The effective dose for the suspension is about the same as that for the tablet.

The prescribing information for Paxil® can be used as a guidance for both dosage and formulation of the paroxetine HCl of the present invention.

Instrumentation used

HPLC was performed on a XTERRA RP18 (5 um; 250 x 4.6 mm), reverse phase column with diammonium- hydrogen-phosphate buffer solution: acetonitrile mixture as gradient

eluent. Detected by U.V. spectroscopy at $\lambda = 285$ nm.

EXAMPLES

Example 1

Preparation of paroxetine HCl with a buffer

An aqueous solution of ammonium chloride (2 grams) in water (5ml) was added to a solution of paroxetine base (5 grams) in toluene (25ml). The reaction mixture was intensively stirred at ambient temperature while concentrated HCl was added in such manner that the pH of the reaction mixture stayed between 3.5 and 8. The stirring was continued for 1 hour. A precipitate formed which was filtered and then washed with toluene and water. The resulting material was dried at a temperature of 60°C under vacuum to give 4.9 grams of paroxetine HCl.

To test the purity of the final product, a 2 mg/ml solution of paroxetine HCl was prepared in a mixture of 0.05M di-Potassium hydrogen phosphate buffer and 35% of acetonitrile. The solution did not develop a pink color after standing for 20 minutes.

Example 2

Preparation of paroxetine HCl with a buffer and an HCl molar equivalent of less than 1

A solution of ammonium chloride (21.6 grams) in water (80 mL) was added to a solution of paroxetine base (53.2 grams), toluene (480 mL) and propyleneglycol monomethyl ether (PGME) (80 mL). HCl (15.7 grams, 0.85 equivalent, 32%) was then added. The mixture was cooled to 2-3°C, and stirred for 2.5 hours at this temperature (pH of water phase of reaction mixture was 7.5). The formed precipitate was filtered, washed with water and toluene, and dried at a temperature of 60°C under vacuum to give 48 grams of paroxetine. The content of the impurity at RRT about 1.5 after storage for 4 days at 55°C was .02.

Example 3

Preparation of paroxetine HCl without a buffer and an HCl molar equivalent of about 1

Example 2 was repeated, except the amount of HCl used was 18.5 grams (1

equivalent). The pH of the aqueous phase of the reaction mixture was about 1. The content of the impurity in the product (49.8 grams) after storage for 4 days at 55°C was 0.23.

Example 4

Preparation of paroxetine HCl in the presence of ascorbic acid

Concentrated HCl (2.43 grams) was added to a solution of paroxetine base (5.6 grams) and ascorbic acid (84 mg) in toluene (56 ml). The reaction mixture was stirred at room temperature for 30 minutes, and subsequently cooled to a temperature of 2-4°C. The mixture was kept at this temperature for about 1.5 hour. A precipitate formed. The formed precipitate was filtered, washed with toluene (5 ml) and water (5ml), and dried at 60°C under vacuum to give paroxetine HCl of white color (approximately 5 grams).

Example 5

Recrystallization of Paroxetine HCl in the presence of ascorbic acid and active carbon.

Paroxetine HCl (approximately 4 grams) was dissolved in toluene(40 ml) at reflux. Ascorbic acid (40 mg) and active carbon SX1 (200 mg) were added to the solution and stirred for 5-10 minutes. The solution was then filtered. The filtrate was cooled to 2-4°C, stirred for approximately 1 hour and filtered again to separate a formed precipitate. The solid precipitate was washed with toluene (4 ml) and dried at a temperature of 60°C under vacuum to give white (color-free) product (3.4 grams). The product was color-free during storage for at least one month at a temperature of 55°C, and yielded solutions (carried out in the same manner as example 1) that were also color-free.

Example 6

Preparation of Paroxetine HCl hemihydrate crystals

Paroxetine HCl crude (40g), acetone (400ml) and methanol (20ml) and ascorbic acid (0.2g) are added to a 1L flask. The mixture is heated to reflux, resulting in a solution. The stirring is continued for 15 minutes, after which the hot solution is filtered through a charcoal bed. The filter cake is washed with 5ml of a mixture acetone/methanol (20:1). The combined filtrates are cooled at 2-3°C and stirred for 1.5 hours. The precipitate is

filtered, washed with acetone (40ml) and dried to give 35g of paroxetine HCl hemihydrate crystals.

Having thus described the invention with reference to particular preferred embodiments and illustrative examples, those in the art can appreciate modifications to the invention as described and illustrated that do not depart from the spirit and scope of the invention as disclosed in the specification. The Examples are set forth to aid in understanding the invention but are not intended to, and should not be construed to, limit its scope in any way. The examples do not include detailed descriptions of conventional methods. Such methods are well known to those of ordinary skill in the art and are described in numerous publications. All references mentioned herein are incorporated in their entirety.

CLAIMS

What is claimed is:

1. A process for preparing paroxetine HCl comprising reacting paroxetine base with less than about one molar base equivalent of HCl and separating the paroxetine HCl, thereby providing a paroxetine HCl substantially free of pink-colored compounds or the amount of an impurity identified by an HPLC RRT of about 1.5.
2. The process of claim 1, wherein the ratio of the HCl to the paroxetine base is from about .75 to about .95 base equivalent.
3. The process of claim 2, wherein the ratio is from about .80 to about .90 base equivalent.
4. The process of claim 3, wherein the ratio is about .85 base equivalent.
5. The process of claim 1, wherein the reaction has a pH of from about 3 to about 8.
6. The process of claim 5, wherein the reaction takes place in a buffer.
7. The process of claim 6, wherein the buffer is a weak acid created by adding ammonium chloride to an aqueous medium.
8. The process of claim 1, wherein at least a portion of the process is carried out in the presence of an effective amount of an anti-oxidant and optionally active carbon.
9. The process of claim 8, wherein the anti-oxidant is ascorbic acid.
10. The process of claim 1, further comprising re-crystallizing the paroxetine HCl in the presence of an effective amount of an anti-oxidant and optionally active carbon.
11. The process of claim 10, wherein the anti-oxidant is ascorbic acid.
12. The process of claim 1, further comprising recrystallizing the paroxetine HCl from a mixture of methanol and acetone.
13. The process of claim 12, wherein the recrystalization is carried out in the presence of an effective amount of an anti-oxidant and optionally active carbon.
14. The process of claim 13, wherein the anti-oxidant is ascorbic acid.
15. The paroxetine HCl prepared by the process of claim 1.
16. A process of preparing paroxetine HCl comprising contacting paroxetine base with HCl at a pH of from about 3 to about 8, and separating the paroxetine HCl, thereby providing a paroxetine HCl substantially free of pink-colored compounds or the amount of an impurity identified by an HPLC RRT of about 1.5.

17. The process of claim 16, further comprising re-crystallizing the paroxetine HCl in the presence of an effective amount of an anti-oxidant and optionally active carbon.

18. The process of claim 16, further comprising re-crystallizing the paroxetine HCl from a mixture of acetone and methanol.

19. The process of claim 16 or 18, wherein at least a portion of the process is carried out in the presence of an effective amount of an anti-oxidant and optionally active carbon.

20. The process of claim 16, wherein molar ratio of the HCl used is less than about one base equivalent.

21. The paroxetine HCl prepared by the process of claim 16.

22. A process of preparing paroxetine HCl comprising contacting paroxetine base with HCl in a buffer and separating the paroxetine HCl, thereby providing a paroxetine HCl substantially free of pink-colored compounds or the amount of an impurity identified by an HPLC RRT of about 1.5.

23. The process of claim 22, wherein the reaction is buffered with a weak acid.

24. The process of claim 23, wherein the weak acid is a result of addition of ammonium chloride to an aqueous medium.

25. The process of claim 22, wherein the paroxetine base is contacted with less than about 1 molar equivalent of HCl.

25. The paroxetine HCl prepared by the process of claim 22.

26. A process for preparing paroxetine HCl comprising converting paroxetine base to paroxetine HCl, and separating the paroxetine HCl, wherein at least a portion of the process is carried out in the presence of an effective amount of an anti-oxidant, thereby providing a paroxetine HCl substantially free of pink-colored compounds or the amount of an impurity identified by an HPLC RRT of about 1.5.

27. The process of claim 26, wherein the anti-oxidant is selected from the group consisting of ascorbic acid, BHT and BHA.

28. The process of claim 27, wherein the amount of ascorbic acid used is from about 0.05% to about 10% weight of paroxetine HCl.

29. The process of claim 28, wherein the ascorbic acid is from about 0.1% to about 10% weight of paroxetine HCl.

30. The process of claim 26, wherein paroxetine base is converted to paroxetine HCl by contacting paroxetine base with less than about one base equivalent of HCl.

31. The process of claim 30, wherein the conversion takes place from a pH of from about 3 to about 8.

32. The process of claim 31, wherein the pH is buffered.

33. The process of claim 26, further comprising recrystallizing the paroxetine HCl in the presence of an effective amount of an anti-oxidant.

34. The process of claim 26, further comprising recrystallizing paroxetine HCl from a mixture of methanol and acetone.

35. The process of claim 34, wherein the re-crystallization is carried out in the presence of an effective amount of an anti-oxidant.

36. The paroxetine HCl prepared by the process of claim 26.

37. A process for preparing paroxetine HCl comprising the steps of:

a) reacting paroxetine base with less than about 1 molar equivalent of HCl in the presence of ammonium ions;

b) crystallizing the paroxetine HCl in the presence of an effective amount of an anti-oxidant and optionally active carbon;

c) separating the paroxetine HCl; and

d) re-crystallizing the paroxetine HCl, optionally in the presence of an anti-oxidant.

38. The process of claim 37, wherein the re-crystallization is carried out from a mixture of acetone and methanol.

39. The process of claim 37, wherein the anti-oxidant is ascorbic acid.

40. A process for preparing paroxetine HCl comprising the steps of:

a) reacting paroxetine base with less than about 1 molar equivalent of HCl;

b) crystallizing the paroxetine HCl in the presence of an effective amount of an anti-oxidant and optionally active carbon;

c) separating the paroxetine HCl; and

d) re-crystallizing the paroxetine HCl, optionally in the presence of an anti-oxidant.

41. The process of claim 40, wherein the re-crystallization is carried out from a mixture of acetone and methanol.

42. The process of claim 40, wherein the anti-oxidant is ascorbic acid.

43. Paroxetine HCl characterized by a having about 0.1% or less of an impurity identified by an HPLC RRT of about 1.5.

44. Paroxetine HCl characterized by less than about 0.22 of an impurity identified by an HPLC RRT of about 1.5 after storage for at least four days at a temperature of about 55°C, and that upon visual inspection does not appear pink.

45. The paroxetine HCl of claim 44, wherein the impurity is less than about .12

46. The paroxetine HCl of claim 45, wherein the impurity is less than about .02.

47. The paroxetine HCl of claim 43 or 44, wherein the paroxetine HCl does not appear pink upon visual inspection.

48. The paroxetine HCl of claim 43 or 44 wherein the paroxetine HCl is paroxetine HCl hemihydrate.

49. The paroxetine HCl of claim 43 or 44, wherein the paroxetine HCl is paroxetine HCl anhydrate.

50. The paroxetine HCl of claim 43 or 44, wherein the paroxetine HCl is a solvate of a solvent selected from the group consisting of isopropanol, 1-propanol, ethanol, acetic acid, pyridine, acetonitrile, acetone, butanone, tetrahydrofuran and toluene.

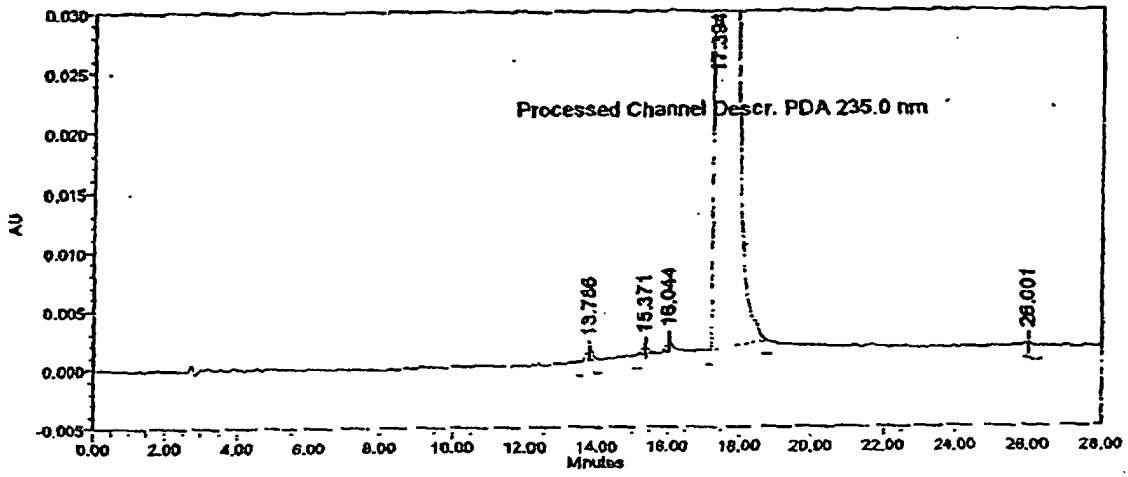
51. A pharmaceutical composition of paroxetine HCl comprising an effective amount of paroxetine HCl of claim 43 or 44, and a pharmaceutically acceptable excipient.

52. A method for inhibiting the re-uptake of serotonin in a mammal in need thereof comprising administering the pharmaceutical composition of claim 51.

53. A method for treating a disease or syndrome selected from the group consisting of depression, Parkinson's disease, anxiety disorders, obsessive-compulsive disorders, panic disorder, post-traumatic stress disorder and PMS comprising administering the pharmaceutical composition of claim 51.

Figure 1

Injection Volume 20.00 ul
Channel 996
Run Time 40.0 Minutes
Label



Peak Results

	Name	RT	Area	% Area	Height
1		13.786	11661	0.08	869
2		15.371	8580	0.06	596
3		16.044	11113	0.07	897
4		17.394	15346928	99.78	871551
5		26.001	2857	0.02	230

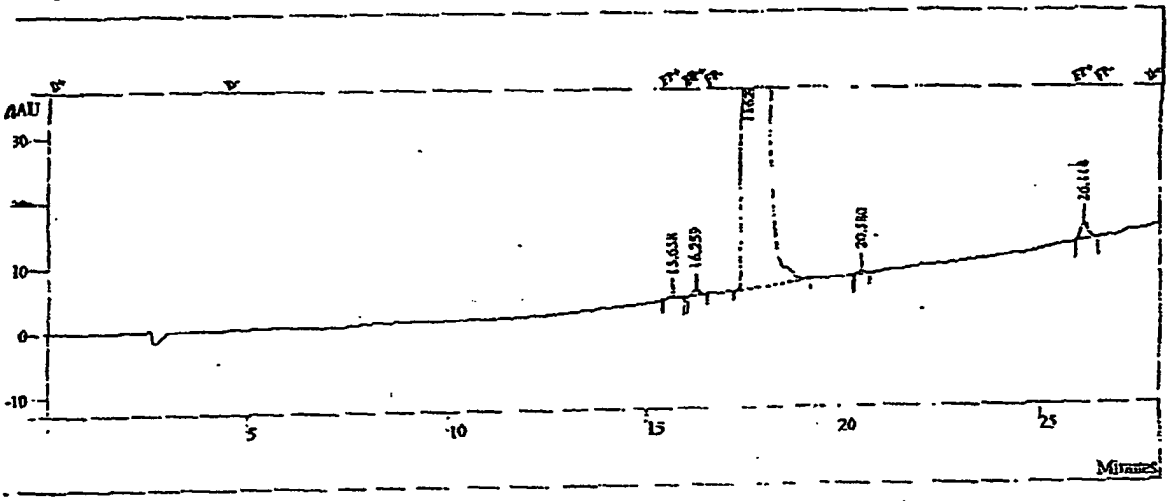
HPLC-1

Figure 2

Sample Prep Info

Loop Size: 20 ul Fill Volume: 20 ul Injection Volume: 20 ul

Run Time (min): 39.983
Sample Rate (Hz): 10.000
Detector Type: 9050



Peak No	Ret. Time (min)	Result ()	Peak Name	Area (counts)	Rel Ret Time	Sep. Code	Width 1/2 (sec)
1	15.658	0.052		3632	0.00	BB	15.4
2	16.259	0.072		5029	0.00	BB	13.7
3	17.626	99.609		6996793	0.00	BB	18.0
4	20.580	0.042		2920	0.00	BB	15.3
5	26.118	0.226		15886	0.00	BB	12.6
		100.001	Totals	7024260			

Status Codes:
U - User defined peak endpoint(s)

Peak Reject Value:	500.000	Multiplier:	1.000
Noise Before Run:	137 microAU	Divisor:	1.000
Noise Used:	137 microAU	Unident. Peak Factor:	0.000
Noise Source:	monitored before this run	Identified Peaks:	7024259
Rejected Peaks:	0	Unidentified Counts:	0
		Detected Peaks:	5

HPLC-2

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/19016

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : A61K 31/445, C07D 405/12
US CL : 514/321, 546/197
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/321, 546/197

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CA 2,187,128 A1 [MURTHY ET AL] 04 April 1998(04.04.98), see entire documents, especially pages 3-6 examples.	15, 21, 25, 36, 43-53
Y	CA 2,193,939 A1 [MURTHY ET AL] 24 June 1998(24.06.98), see entire document, especially pages 3-5 examples.	15, 21, 25, 36, 43-53
Y	US 5,672,612 A [RONSEN ET AL] 30 September 1997(30.09.97), see entire document, especially col. 3-4 examples 1-2, claim 1.	15, 21, 25, 36,43-53
Y	EP 0,810,224 [ASAHI GLASS COMPANY LTD.] 30 May 1997(30.05.97), see entire document, especially column 3-4, examples 1-6.	15, 21, 25, 36, 43-53
X --- Y	WO 00/32593 A1 [SMITHKLINE BEECHAM PLC] 8 June 2000(08.06.00), see entire document, especially p.2 lines 12-17 and p.6, example 6.	1-7, 15, 16, 21, 22, 25, 43-53 --- 1-53
Y	WO 98/01424 A1 [RICHTER GEDEON VEGYESZETT GYAR RT] 15 January 1998(15.01.98), see entire document, especially22-23 example 22.	1-7, 15, 16, 21, 11, 25, 43-53
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Y	US 5,872,132 A [WARD ET AL] 16 Feburary 1999(16.02.99), see entire document, especially column 4, lines 8-29 and examples.	12, 18, 34, 38, 41

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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INTERNATIONAL SEARCH REPORT

C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 99/55698 A1 [SMITHKLINE BEECHAM PLC] 04 November 1999(04.11.99), see entire document.	8-11, 13-14, 17, 19, 27-29, 33, 35, 37, 39, 40, 42

INTERNATIONAL SEARCH REPORT

PCT/US02/19016

Continuation of B. FIELDS SEARCHED Item 3:
CAS--structure, paroxetine, ascorb?, impurity, color
EAST/WEST--subclass, image, paroxetine, ascorb$, impurity, color

Application of Two-Dimensional ^{13}C Solid-State NMR to the Study of Conformational Polymorphism

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Abstract: Two-dimensional ^{13}C solid-state nuclear magnetic resonance (2D SSNMR) spectroscopy was applied to the study of three conformational polymorphs of 5-methyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile. The separation of sidebands by order experiment (de Lacroix, S. F.; Titman, J. J.; Hagemeyer; A.; Spiess, H. W. *J. Magn. Reson.* **1992,** *97,* 435−443) allowed the separation of isotropic and anisotropic chemical shift information over two dimensions, making it possible to distinguish individual carbon atoms and analyze the full chemical shift anisotropy patterns using magic angle spinning (MAS) at moderate spinning speeds. The C-3 carbon of the thiophene ring, α to the nitrile carbon, was chosen to probe the differences in chemical environment between forms. The three forms exhibited a large variation in both measured and theoretically predicted isotropic and anisotropic chemical shifts for this carbon site. The results summarized in this paper demonstrate the utility in using 2D SSNMR methods for studying polymorphism in crystalline compounds with moderate molecular weights.

Introduction

A number of organic solids exhibit conformational polymorphism.[1] Conformational polymorphs have the same chemical structure, but differ in molecular conformation. Polymorphism is especially important in pharmaceutical solids since polymorphs typically exhibit differences in stability and bioavailability. Since conformational differences can result in variations in intramolecular distances and local electronic structure, NMR is an ideal and sensitive probe for this type of behavior and can provide complementary information to that obtained from other structural techniques, such as X-ray methods. One way in which NMR can be used to detect conformational differences is by observing changes in the chemical shift. In addition to the isotropic chemical shift information that can be measured in a liquid-state NMR experiment, solid-state NMR allows the measurement of chemical shift anisotropy (CSA), which provides additional structural information. CSA is a second rank tensor interaction that arises in solid samples from a dependence of the chemical shift on molecular orientation with respect to the external static magnetic field. Using SSNMR to study molecular structure and conformation through CSA currently is of growing interest and can be aided by the concurrent use of ab initio methods.[2] Toward the study of polymorphism, a number of studies have used 1D CPMAS to observe structural changes through the CSA tensor.[3] However, even in moderately complex organic solids the overlapping spectral features make analysis nearly impossible, even with the application of very high spinning speeds.

To remedy this situation, a number of schemes have been developed to separate isotropic and anisotropic chemical shift information under magic angle spinning (MAS) conditions.[4−16] The easiest of these to implement is the 2D NMR experiment in which the isotropic and anisotropic information can be obtained simultaneously for each distinct site in the sample, without special hardware requirements. An example of such an experiment is the 2DTOSS[17] pulse sequence developed by Spiess and co-workers which separates CSA information by sideband order in the indirectly detected frequency dimension and provides the full CSA patterns in the second dimension.[14]

* To whom correspondence should be addressed.

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(2) See, for example: (a) Havlin, R. H.; Le, H. B.; Laws, D. D.; deDios, A. C.; Oldfield, E. *J. Am. Chem. Soc.* **1997,** *119,* 11951. (b) Heller, J.; Laws, D. D.; Tomaselli, M.; King, D. S.; Wemmer, D. E.; Pines, A.; Havlin, R. H.; Oldfield, E. *J. Am. Chem. Soc.* **1997,** *119,* 7827. (c) Liu, F.; Orent, A. M.; Alderman, D. W.; Grant, D. M. *J. Am. Chem. Soc.* **1997,** *119,* 8981. (d) Orendt, A. M.; Hu, J. Z.; Jiang, Y. J.; Facelli, J. C.; Wang, W.; Pugmire, R. J.; Ye, C. H.; Grant, D. M. *J. Phys. Chem. A* **1997,** *101,* 9169.

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Published on Web 10/30/1998

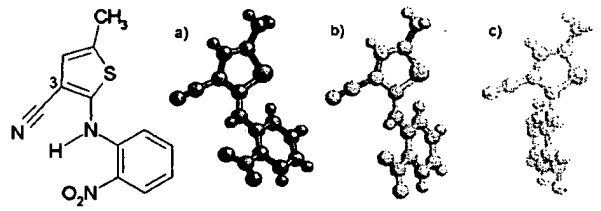

Figure 1. Chemical structure and three forms of 5-methyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile, collectively referred to as ROY. (a) Yellow form with a phenyl-thiophene coplanar angle of approximately 106°, (b) orange form with a coplanar angle of 56°, and (c) the red form with a coplanar angle of 46°. The number "3" is placed near the C-3 carbon to indicate that this is the probe nucleus of interest.

The previous application of this technique was dedicated to the study of amorphous polymers, but the sequence is also quite useful for studying crystalline materials.

In this paper we report our experiments using the 2DTOSS sequence to analyze three crystalline polymorphic forms of 5-methyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile, which we believe constitutes the first application of 2D SSNMR to the study of conformational polymorphism. This compound has five known polymorphic forms, three of which are shown in Figure 1 and are known collectively as ROY due to their red, orange, and yellow colors. The major structural difference in these compounds is the coplanar angle between the phenyl and thiophene rings. The form with the largest coplanar angle, 106°, is yellow in color, the next largest, 56°, is orange, and the smallest, 46°, is red.[18] The ROY compounds have been previously characterized using X-ray diffraction, FTIR, and CPMAS NMR.[18] The ^{13}C CPMAS spectra indicate that the thiophene carbon α to the nitrile carbon, referred to as C-3, has an isotropic peak that is isolated from the other resonances and differs noticeably between polymorphic forms. For these reasons, we chose to focus on this carbon as a probe for the conformational differences between the polymorphs. Future work in our laboratory will investigate the other carbon sites. The ROY compound has a total of 12 chemically distinct carbon sites, making the 1D CPMAS spectra complicated by dozens of spinning sidebands in a spinning regime slow enough for sideband analysis. The ROY compounds are therefore ideal for demonstrating the utility of the 2DTOSS sequence for studying polymorphism. In addition to our NMR work, we have also applied density functional methods to compare observed and predicted conformational dependencies of the chemical shifts and to investigate a possible origin for these dependencies.

Experimental Section

All polymorphic forms of 5-methyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile were gifts from Eli Lilly and Company and had ^{13}C in natural abundance (1%). The yellow form is readily grown from a slurry of any other form at room temperature. The red form is obtained by crystallization from ethanol at a concentration of about 70 mg/mL. The orange form can be grown from ethanol or by slow evaporation from methanol.

The 2DTOSS pulse sequence is illustrated in Figure 2 and is described in detail by de Lacroix et al.[14] Briefly, the preparation period begins with ^1H to ^{13}C cross-polarization to generate transverse ^{13}C magnetization. A TOSS (TOtal Suppression of Sidebands) sequence,[5] consisting of a series of four specially timed π pulses, is then applied to rotate the magnetization trajectory of each crystallite so that each

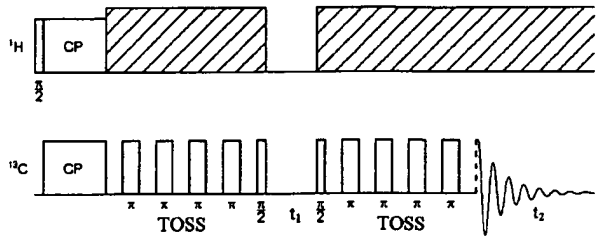

Figure 2. 2DTOSS sequence developed by de Lacroix et al. A detailed description of this sequence can be found in refs 14 and 20.

trajectory has the same time-averaged position.[19] As a result, TOSS generates a net magnetization vector that would effectively precess at only the isotropic chemical shift frequency by imparting to each crystallite a phase that is dependent on its position in the rotor and its orientation in the external static magnetic field. Immediately after the first TOSS period, one component (x or y) of the magnetization is stored along the z-axis with a $\pi/2$ pulse and the ^1H decoupling is turned off in order to eliminate any remaining magnetization in the $x-y$ plane. The other component of the magnetization is measured in a second experiment, and the two components are combined in the hypercomplex data processing. Since the magnetization is aligned along z during t_1, no isotropic chemical shift evolution takes place during this time period. However, each crystallite does accumulate a rotor dependent phase of $\omega_r t_1$, where ω_r is the spinning speed, which affects the orientational-dependent anisotropic chemical shift frequency during t_2. Following the t_1 delay, a $\pi/2$ pulse returns the magnetization to the transverse plane, and a second TOSS sequence is executed. The phase of the magnetization for a given crystallite just prior to acquisition is correlated to the amount of rotor phase accumulated during the t_1 period. By accumulating data spaced equally over one rotor cycle, the full spinning sideband manifold is reconstructed in the ω_1 dimension without contributions from the isotropic chemical shift. For organic solids, T_1 is usually much longer than $1/\omega_r$; thus, in effect, the modulation in t_1 is essentially fully periodic. It is therefore sufficient to use only as many t_1 increments as sidebands desired in the ω_1 dimension, spacing the t_1 timings in regular increments over one rotor period. The resulting 2D FID has purely anisotropic modulation in t_1 and the full chemical shift modulation in t_2. Fourier transformation of the 2D data set over the t_2 dimension produces a series of MAS spectra in which each sideband of order N has a pitch or phase of $N\omega_r t_1$. A subsequent transform over the t_1 dimension yields a 2D spectrum that separates the spectra by sideband order in the ω_1 dimension, and produces the full MAS spectrum of each spinning sideband order in the ω_2 dimension.

All of the ^{13}C spectra were recorded on a commercial Varian Unity Plus spectrometer at room-temperature operating at 75.44 MHz with a 7-mm Varian CPMAS probe. Samples were spun at 1500 Hz in each 2DTOSS experiment. Slow spinning speeds were employed to ensure that each CSA pattern had a sufficient number of sidebands for analysis. Proton and carbon 90° pulse widths were 5 μs, and the ^{13}C contact time was 2.5 ms. The TOSS pulse timings used in our experiments had a total duration of 2 rotor cycles per TOSS period.[20] Composite π pulses and a phase cycling scheme were implemented to reduce imperfections in the TOSS sequence.[21,22] A table of pulse phases used in this sequence can be found in ref 14. A total of 16 t_1 increments were recorded, including both the real and the imaginary components of the signal, and at least 135 transients were taken for each t_1 increment. The ROY compounds had long ^1H T_1 times ranging from 30 to 60 s such that recycle delays of 40−70 s were necessary for optimal signal averaging. As a result, each experiment ran for approximately 40 h.

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The isotropic peak assignments in the ^{13}C SSNMR spectra were made by comparison with the corresponding solution phase spectra. All chemical shift values are reported relative to TMS. The chemical shifts were referenced using an internal adamantane standard for which the chemical shift values have been recorded previously.[23]

Experimental CSA tensor values were determined using an iterative fitting program based on the formalism developed by Herzfeld and Berger,[24] and the analysis was performed on a desktop PC. A Simplex routine was used to adjust the fitted tensor values until the numerically calculated sideband intensities agreed well with experimental values.[25] Calculated sideband intensities all fit to within 3% of the volume of the isotropic peak. An error of 3.5 ppm in all measured tensor values was estimated by adjusting tensor values in small increments until the minimum square difference statistic, χ^2_{min}, had doubled.

Theoretical calculations were performed on an IBM RS-6000 computer cluster using the Gaussian 94 program.[26] All of the calculations used a density functional approach with the hybrid B3LYP functional[27,28] and the Gaussian basis set, 6-311G.[29,30] Structures determined by X-ray methods were used as input coordinates for all of the calculations, and the proton positions were relaxed by partial geometry optimizations. NMR shielding calculations were performed with gauge-invariant atomic orbitals.[31] Initially, a constant offset of 190.2 ppm was applied to reference the shielding values to TMS. However, this correction had a noticeable bias toward overestimating large shift values, and thus a linear correlation of $\sigma_{shift} = -0.969\sigma_{shielding} + 182.8$ ppm, obtained from the difference between observed shifts and predicted shieldings for the C-3 tensor values and the methyl isotropic peaks, was applied. Similar linear correlations have recently been used by Grant and co-workers.[2d]

Results

A spectrum generated by the 2DTOSS sequence is shown in Figure 3 for ROY-orange. At the top of the 2D spectrum is a projection of the data along the ω_2 dimension. The projection is equivalent to the standard 1D MAS spectrum and illustrates the need for using a 2D separation experiment for CSA analysis. Each trace along the ω_2 dimension, for a given ω_1, contains the sidebands of order $N = \omega_1/\omega_r$ for each chemically distinct ^{13}C site. The MAS pattern for each resonance resides along a direction parallel to the diagonal in the 2D spectrum. Small contours located outside of these diagonal regions are noise peaks that are larger than the chosen display threshold. As can be seen from the spectrum, sites such as C-3 which have a moderate to large size CSA produce many spinning sidebands at low spinning speeds, and hence have many peaks along the diagonal. Sites with smaller CSA, such as the methyl peak found at $\omega_1 = 0$, $\omega_2 = 18$ ppm, produce almost no sideband intensity.

A 1D MAS spectrum can be constructed for each site by selecting the corresponding sideband peak in each trace along ω_2 and placing the bands together. The result of this process is shown in Figure 4a for the C-3 site of the ROY-orange form. The dashed lines indicate that no information exists between the sidebands due to the manner in which the spectrum was constructed. The CSA tensor values are extracted from the spinning sideband intensities using the fitting process outlined above. An example of a result from this process is shown in Figure 4b for C-3 of the ROY-orange form. A line broadening of 75 Hz was used in the simulated spectrum to match experimental line widths. The fitted CSA tensor values for all of the ROY forms are tabulated in Table 1.

In Figure 5, the isotropic trace from the 2DTOSS spectrum is shown for each of the three polymorphic forms of ROY. The

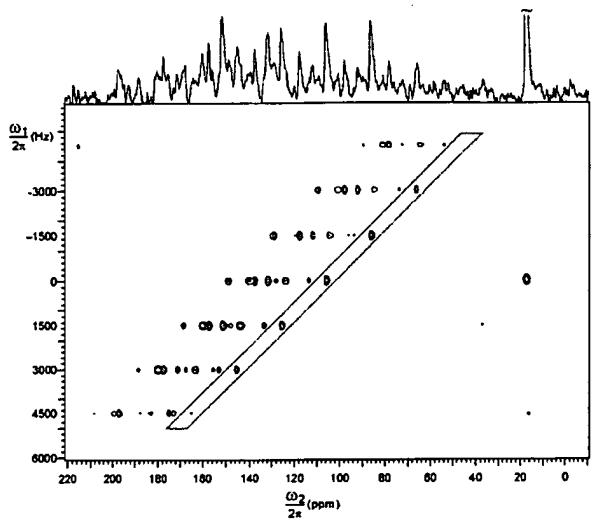

Figure 3. 2DTOSS spectrum of the ROY-orange form. Chemical shift information is separated by sideband order in the ω_1 dimension and by full CSA pattern in the ω_2 dimension. A box is drawn around the peaks that constitute the 1D MAS spectrum for the C-3 site.

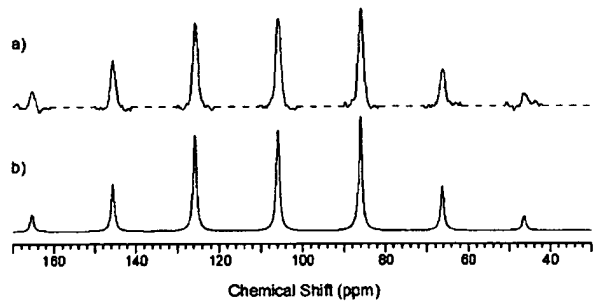

Figure 4. Fit to the 1D MAS spectrum for C-3 in the ROY-orange form. (a) 1D MAS spectrum is constructed by piecing together successive slices of the 2DTOSS spectrum along the ω_1 dimension. (b) Simulated spectrum generated from a best fit to the CSA tensor values.

Table 1. C-3 Site CSA Tensor Values for the Three Forms of ROY Reported in ppm from the ^{13}C Resonance of TMS[a]

form	$\delta_{11}(\sigma_{11})$	$\delta_{22}(\sigma_{22})$	$\delta_{33}(\sigma_{33})$	$\delta_{iso}(\sigma_{iso})$
red	49.2(48.8)	90.7(93.2)	155.0(150.8)	98.3(97.6)
orange	50.2(49.8)	102.7(99.8)	165.7(167.3)	106.2(105.6)
yellow	43.3(44.1)	105.8(107.5)	179.2(180.6)	109.4(110.7)

[a] For the experimentally determined tensor values (the values on the left), the isotropic shifts were obtained from $\omega_1 = 0$ slices of the 2DTOSS spectra and the traceless tensor values were calculated by fitting the MAS sideband intensities. An error of 3.5 ppm in all measured tensor values was estimated by doubling the fitting statistic, χ^2_{min}. In parentheses are the corresponding adjusted tensor values calculated using Gaussian 94.

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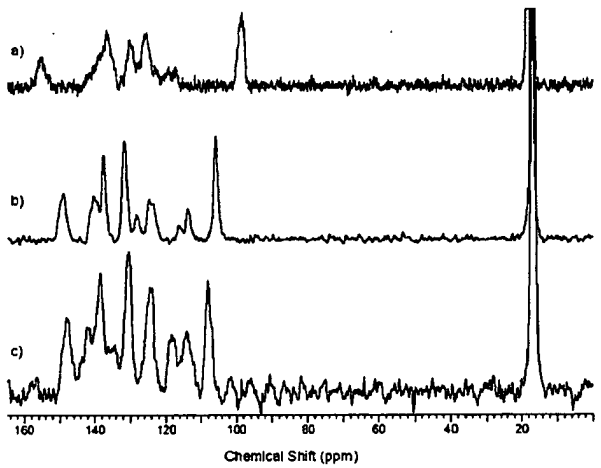

Figure 5. Isotropic spectra obtained by taking $\omega_1 = 0$ slices of the 2DTOSS spectra for ROY (a) red, (b) orange, and (c) yellow. The C-3 site has an isotropic shift of 98 ppm for ROY-red, 106 ppm for ROY-orange, and 109 ppm for ROY-yellow.

$\omega_1 = 0$ trace of a 2DTOSS spectrum is equivalent to the spectrum generated by a 1DTOSS[5] experiment and can be useful for peak assignments and comparisons to liquid-state spectra. Since the 2DTOSS experiment does not rely on rotor speed to produce isotropic spectra, there are no mechanical limitations on which ^{13}C sites can be analyzed due to the magnitude of the CSA.

The results from the density functional analysis of the C-3 chemical shift tensor values are also summarized in Table 1. After application of the linear regression, calculated tensor values matched closely with the observed values, having an rms deviation of only 2.1 ppm.

Discussion

It is readily apparent that both isotropic and anisotropic chemical shifts vary noticeably between polymorphs. Figure 5 illustrates isotropic peak rearrangement in the aromatic region of the spectrum, from 100 to 160 ppm. Isotropic resonances that overlap cannot be separated by the 2DTOSS sequence and therefore many sites in this region are difficult to analyze. The C-3 site, however, is easily distinguishable and appears to be sensitive to the differences in conformation between forms. A gradual progression in its isotropic resonance is observed as the phenyl-thiophene coplanar angle becomes larger in magnitude. The isotropic peak for C-3 moves downfield by almost 10 ppm in going from ROY-red to ROY-yellow. The anisotropic chemical shift also changes in magnitude between forms and appears to be more sensitive to the structural differences than the isotropic chemical shift. The tensor values listed in Table 1 show that the breadth of the CSA for C-3 increases in magnitude by 30 ppm and the line shape appears to become more asymmetric as the coplanar angle increases.

In contrast, some carbon sites in the different forms are not as sensitive to molecular conformation. The methyl peak at 18 ppm, for example, shows little difference in isotropic chemical shift. Unfortunately, the methyl peak yields only small, first-order spinning sidebands at 1500 Hz, making determination of the anisotropic chemical shift by spinning sideband analysis impractical.

One explanation that could account for the difference in chemical shift sensitivity between the C-3 and methyl carbons to the changes in conformation is the transfer of electron density between the phenyl and thiophene rings in the molecules. In an LCAO-MO sense, the p-orbitals of the atoms in the two rings become aligned in the more coplanar polymorphs, which could allow greater transfer of π electrons between the rings, resulting in a net increase in electron density at the C-3 carbon site. Hence C-3 for the ROY-red polymorph would experience the greatest diamagnetic shielding and would be found the furthest upfield. The methyl group, however, would not participate in the transfer of electron density; hence, its resonance would be relatively unaffected by the changes in conformation. A Mulliken charge density analysis[32] at the C-3 nucleus supports this idea. Calculations show that there is an increase in electron density at the C-3 site by as much as 10% of an electron charge, going from the yellow form to the red form. However, the charge density at the methyl carbon site is relatively constant between forms, with differences of less than 1% of a charge unit. The theoretical modeling of the electron density at the C-3 site is partially validated by the close agreement between the experimentally determined and theoretically calculated chemical shift principal tensor values found in Table 1.

Of the various 2D isotropic/anisotropic techniques, we found the 2DTOSS sequence to be the easiest to implement since there is no need for special hardware and the pulse programming is relatively straightforward. Also, since the number of t_1 increments needs only to be as large as the number of sidebands expected in the 1D MAS spectrum, the experiment is relatively short in length compared to other 2D methods. For a molecule with proton $T_1 < 1$s, a 2DTOSS spectrum containing up to third-order sidebands and acquiring 128 scans per t_1 increment would take about 30 min to acquire with natural abundance ^{13}C samples. Due to the low spinning speed requirements for CSA analysis, large sample volume rotors could be used to further decrease the acquisition time.

Conclusions

We have shown that the 2DTOSS experiment, which represents one of a class of isotropic/anisotropic chemical shift separation experiments, comprises a viable method to study conformational polymorphism. By using the 2DTOSS sequence, we were able to readily determine anisotropic chemical shifts, which, for the example of the C-3 carbon site on the ROY compounds, can be more sensitive to molecular conformation than isotropic chemical shifts. This type of information cannot feasibly be extracted from any 1D experiment without isotopically labeling the individual ^{13}C sites.

2D SSNMR is a powerful method for analyzing differences in chemical environment and molecular structure and will provide a new method for determining molecular conformations in polymorphism. By coupling information derived from the application of 2DTOSS experiments with ab initio or density functional methods, quantitative structural information can be obtained. Work in our lab along these lines is progressing to provide a fuller picture of the ROY compounds. Additionally, experiments designed to address the utility of other 2D techniques that provide complementary structural information, such as homonuclear and heteronuclear distances, will be examined in future work and may further expand the applicability of SSNMR for analyzing conformational polymorphism.

Acknowledgment. The authors thank Eli Lilly and Company for the samples used in these experiments. J.S. thanks Eastman Chemical Company for a graduate fellowship. E.M. thanks the NSF for a graduate fellowship. D.R. is a Cottrell Scholar of the Research Corporation.

JA980952T

(32) Szabo, A.; Ostlund, N. S. In *Modern Quantum Chemistry.*; Macmillan: New York, 1982; pp 151, 203.

IN RE KENNETH B. COFER, DECEASED, BY THE SHELL OIL COMPANY, ASSIGNEE

No. 7449

United States Court of Customs and Patent Appeals

53 C.C.P.A. 830; 354 F.2d 664; 1966 CCPA LEXIS 487; 148 U.S.P.Q. (BNA) 268

Oral argument November 2, 1965

January 13, 1966

PRIOR HISTORY: [***1]

APPEAL from Patent Office, Serial No. 14,497

DISPOSITION:

Reversed.

CASE SUMMARY:

PROCEDURAL POSTURE: Appellant challenged decision from the Patent and Trademark Office Board of Appeals affirming the examiner's rejection of claims in appellant's patent application.

OVERVIEW: The examiner rejected appellant's claims for a patent on the basis that the claimed product was merely a different form of a known compound, that the product had the same utility as the art compound, and was therefore unpatentable under *35 U.S.C.S. § 103.* The court found the record failed to support a holding that those skilled in the art should have known that the compound would exist in crystalline form or how to obtain such crystals. The court held that it was improper to presume such knowledge under the circumstances. The court was required to review the facts based upon the material before the Patent and Trademark Office. Facts appearing in the record, rather than prior decisions in and of themselves, were required to support the legal conclusion of obviousness under *35 U.S.C.S. § 103.* Merely stating that a compound or composition was obvious, without adequate factual support, was not sufficient.

OUTCOME: The court reversed the decision because it was improper to presume knowledge of the existence of the crystal.

LexisNexis(R) Headnotes

COUNSEL:

James H. Parker, Edward B. Beale (Martin S. Baer, of counsel) for the appellants.

Clarence W. Moore (Joseph Schimmel, of counsel) for the Commissioner of Patents.

OPINIONBY:

WORLEY

OPINION: [**664]

[*831] Before WORLEY, Chief Judge, and RICH, MARTIN, SMITH, and ALMOND, Jr., Associate Judges

WORLEY, Chief Judge, delivered the opinion of the court:

This appeal is from the decision of the Board of Appeals affirming the examiner's rejection of claims 1 and 8 in appellant's application n1 entitled "High Purity Diepoxide."

n1 Serial No. 14,497, filed March 14, 1960.

The subject matter is reflected in claims 1 and 8:

1. As a manufacture, free-flowing crystals of 2,2-bis (2,3-epoxypropoxyphenyl) propane.

8. As a manufacture, free-flowing crystals of substantially pure 2,2-bis (2,3-epoxypropoxyphenyl) propane characterized by a sharp melting point of about 43.5 degrees C, a weight-to-epoxide ratio of about 170 grams per gram [***2] equivalent epoxide, total chlorine content of less than 0.1 percent by weight, saponifiable chlorine content of less than 0.01 percent by weight, total hydroxyl content and phenolic hydroxyl content of less than 0.01 gram equivalents per 100 grams, each, and a viscosity, when a supercooled liquid, of less than about 40 poises at 25 degrees C.

The compound of the claims, 2,2-bis(2,3-epoxypropoxyphenyl) propane [also known as the diglycidyl ether of 2,2-bis(4-hydroxyphenyl) propane and hereinafter termed 2,2-B] is well known to those skilled in the art as useful in the [**665] preparation of thermosetting [*832] epoxy resins. The compound is the simplest member (n=O) of a family of diepoxides of the formula

[Graphic omitted. See illustration in original.]

Those compounds are produced by the reaction of epichlorohydrin with 2,2-bis (4-hydroxphenyl) propane, the latter compound also being known as "Bisphenol A." The simplest addition product formed in that reaction is 2,2-B, resulting from a combination of two parts epichlorohydrin and one part "Bisphenol A." Higher molecular weight diepoxides which contain epichlorohydrin and "Bisphenol A" in ratios of 3:2, 4:3 and [***3] the like, are also formed in that reaction. By appropriate control of the ratio of epichlorohydrin to "Bisphenol A" in the reaction, complex liquid mixtures which contain a relatively high proportion of 2,2-B, e.g. 70% to 90% of the total reaction product, can be produced. According to appellant's specification no method has yet been described which permits production of pure 2,2-B directly by the reaction of epichlorohydrin with "Bisphenol A." Prior attempts to recover 2,2-B have resulted only in recovery of a relatively viscous liquid containing impurities which adversely affected the usefulness of epoxy resins prepared therefrom.

Appellant has found that substantially pure 2,2-B is capable of existing in crystalline form and can be recovered from certain concentrates of the compound using controlled crystallization methods. n2 The free-flowing crystals are disclosed to be advantageous with respect to handling convenience and, when combined with the usual amine or anhydride curing agents, are said to produce thermoset epoxy resins equal or superior to those produced from the liquid 2,2-B compositions.

n2 The examiner stated that "the Patent Office has recognized his contribution to the art by allowing claims drawn to methods of crystallizing and recovering" crystalline 2,2-B in other patent applications.

[***4]

The references are:

Werner et al	2,467,171	Apr. 12, 1949
Bender et al	2,506,486	May 2, 1950
Havens	2,530,353	Nov. 14, 1950

Dearborn et al., Ind. and Eng. Chem., Volume 45, pages 2715-21 (1953).

Werner, Bender and Dearborn all name the compound 2,2-B and characterize it as a liquid. Werner, for example, discloses that both stereoisomers of 2,2-B were recovered in the form of "water white somewhat viscous liquids." Bender discloses a 90.6% concentrate of 2,2-B to be a "viscous liquid (5000 centipoises at 25 degrees C.)." Dearborn [*833] states that epoxy resins having the structure depicted earlier in this opinion are "liquid or solid depending on the degree of polymerization, indicated by n," and that 2,2-B is an "amber liquid." Havens discloses 2,2-B as a stabilizer for resins.

Up to the time of his Answer, the examiner's rejection of the claims appears to have been founded on two separate grounds. In the final rejection the examiner stated:

Claim 1 is again rejected as unpatentable over Werner et al, * * * Dearborn et al, Havens and Bender et al, all of record and which disclose the diglycidyl ether of Bis-phenol A. Whether or not applicant [***5] considers the free flowing [**666] crystals of the claimed compound as a product of manufacture or as a compound per se is immaterial; the fact remains that crystalline 2,2-bis (2,3-epoxypropoxyphenyl) propane is deemed to be obvious as merely directed to an old compound in a crystalline form. * * * Furthermore, although the art cited does not specifically teach the production of the crystalline compound the art does teach the production of other closely related glycidyl ethers of hydroxy phenylalkanes, in crystalline forms and therefore it is deemed to be suggested that the crystalline form of this glycidyl ether would exist in crystalline form under sufficiently conducive conditions. The claimed crystalline compound is thus rendered obvious, *35 USC 103.*

In subsequent traversal of the examiner's position that the existence of closely related glycidyl ethers of hydroxyphenylalkanes in crystalline form would suggest that 2,2-B, the diglycidyl ether of 2,2-bis(4-hydroxyphenyl) propane, would also exist in crystalline form, appellant filed an affidavit of one Kelly to demonstrate that other glycidyl ethers bearing close relationship to 2,2-B do not exist in crystalline form. [***6]

Subsequently, in his Answer, the examiner said:

Claims 1 and 8 stand subject to the Final Rejection as lacking invention over any of the Werner et al, Havens, Bender et al or Dearborn et al references, all of which disclose the claimed compound in its normal form, viz, a viscous liquid.Appellant does not dispute this. The claims are directed to a more pure form of the disclosed compound which has been made to crystallize and is claimed in its crystalline form as a manufacture. The claimed compound is not patentable because it is taught by the prior art and is obvious, *35 USC 103.* * * *

* * *

The basis for the rejection is, essentially, that the claimed product is merely a different form of a known compound, and, notwithstanding that some desirable results are obtained therefrom, since the product has the same utility as the art compound; the claimed product is deemed to be unpatentable thereover. * * *

* * *

The Examiner's suggestion in the Final and Advisory actions given with respect to the obviousness of the instant crystallized product, because of the fact that analogous compounds are known to exist in crystalline form, * * * is withdrawn as being superfluous and [***7] not determinative of the essential issues involved in this case. The affidavit of * * * Kelly submitted by applicant * * * is consequently considered to be moot, as the behavior of analogous [*834] compounds with regard to susceptibility of crystallization of the instant compound is considered to have no controlling bearing upon the essential issues of this case. From a factual viewpoint, for whatever it is worth, applicant has shown that four related compounds are not susceptible to crystallization by the methods employed whereas the art shows that certain other related compounds are normally recoverable in the crystalline form.

The board was of the view, and we agree, that:

The sole determinative issue here is whether the claimed product, which is free-flowing and crystalline in form, is obvious, under *35 U.S.C. 103,* where the prior art discloses the same compound in its normal form, i.e., as a viscous liquid.

The board observed that:

Appellant points to the various advantages of his product as compared to the prior art compound, such as better color, high epoxy content, [**667] lower impurity content, easier to handle in preparing epoxy resins therefrom, better [***8] electrical properties, and long shelf life. * * *

After a brief discussion of the respective contentions of the examiner and appellant, the board referred to its decision in *Ex Parte Hartop, 139 USPQ 525,* as "clearly apposite to the present factual situation," stating:

* * * We note that the decisions relied on herein, by both the appellant and the Examiner, are discussed therein, and we deem it unnecessary to discuss these again. The conclusion reached therein to the effect "that merely changing the form, purity or another characteristic of an old product, the utility remaining the same as that for the old product, does not render the claimed product patentable," is clearly applicable to the factual situation herein, and we will accordingly adopt it here. As pointed out by the Examiner, the prior art resins in viscous liquid form, have the same utility as the claimed crystalline compound, viz., for use in the preparation of synthetic resins, the difference in properties, therebetween resulting only from a greater degree of purity, and, therefore, to be expected. [Emphasis supplied.]

Appellant argues that his claims have been rejected solely because his new manufacture [***9] is said to have "the same utility" as the known liquid, and that the record is devoid of any express support for a finding by either the examiner or board that the new physical form of 2,2-B would be obvious. He urges that the board did not give sufficient weight to the pertinent facts of this case, but held, as a matter of law, that a free-flowing crystalline form of a product heretofore known only as a liquid would be obvious under *35 USC 103.*

[1] We think the record supports those contentions. There is no explanation in the views of the board or examiner why it should be found from the references or from common knowledge that a person skilled in the art would regard free-flowing crystals of 2,2-B to be obvious. In such circumstances, we are not free to search for speculative reasons that might support the rejection, when it is apparent from those opinions that Werner, Bender and Dearborn were ultimately used only to show that 2,2-B was known as a viscous liquid, [*835] and not to suggest that the crystalline form would also exist. Indeed, the examiner withdrew his initial finding that the cited prior art would suggest that 2,2-B could exist as crystals after the Kelly [***10] affidavit was filed. The board did not discuss that phase of the original rejection.

[2] The board seemingly regarded the question whether appellant's product had the same or different utility as dispositive of the issue here, relying on the discussion of prior case law in Hartop. We see no need to review the cases relied on there save that each case must stand on its own facts. The cited cases fail to support the broad proposition that

* * * merely changing the form, purity or another characteristic of an old product, the utility remaining the same as that for the old product, does not render the claimed product patentable. * * *

We think examination of the decisions relied on here in Hartop will demonstrate that the materials involved therein were found unpatentable where the alleged difference in form or purity of those substances was either disclosed or inherent in, or rendered obvious by, the prior art of record. n3 Necessarily it is facts appearing in the record, rather than prior decisions in and of themselves, which must support the legal conclusion of obviousness under *35 USC 103.* Merely stating that a compound or composition is obvious, without adequate factual [***11] support, is not sufficient.

[4] To be sure, whether a given chemical compound or composition has the same usefulness as closely related materials may be an important consideration in determining obviousness under *35 USC 103.* But it is only one consideration. [**668] We think the board failed to address itself to other factors which must be given weight in determining whether the subject matter as a whole would have been obvious, namely, whether the prior art suggests the particular structure or form of the compound or composition as well as suitable methods of obtaining that structure or form. The new form of the compound set forth in the claims is as much a part of the "subject matter as a whole" to be compared with the prior art as are other properties of the material which make it useful.

[5] Apparently recognizing the dificiency in the record before us, the solicitor has devoted a considerable portion of his brief to reasons, accompanied by references to a textbook, which purport to establish obviousness of the crystalline form of 2,2-B and the techniques employed in obtaining the crystals. We look upon those contentions as but an attempted revival of the arguments [***12] which were abandoned by the examiner and not mentioned by the board.The solicitor's reliance here on an allegedly standard textbook on chemistry as further support for the Patent Office position illustrates a growing tendency on the part of appellants and the Patent [*836] Office alike to impair the clear and specific language of *35 USC 144,* which requires us to determine the appeal "on the evidence produced before the Patent Office." Insofar as the record shows, that textbook was not the subject of discussion between appellant and the Patent Office, hence is not such "evidence." We would remind counsel for all parties that the record upon which they must stand or fall on review here is that which is made in the Patent Office. In most cases, particularly in the chemical field, appeals are sufficiently complex without counsel on either side bringing in, at this late date, technical data which, if relevant, should have been submitted below. Nor do we think it appropriate in the present case to take judicial notice of that textbook, for it appears to relate to a highly technical and empirical area of chemistry and we have no independent way of evaluating its repute and notoriety [***13] in the art.

We find the record fails to support a holding that those skilled in the art should have known that 2,2-B would exist in crystalline form or that it would be known how to obtain such crystals. We think it improper to presume such knowledge under the circumstances. *In re Williams, 36 CCPA 756, 171 F.2d 319, 80 USPQ 150.* Compare *In re Adamson, 47 CCPA 839, 275 F.2d 952, 125 USPQ 233.*

The decision is reversed.